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ASSESSMENT OF SPATIOTEMPORAL CHANGES OF PAIN AND SENSORY PERCEPTIONS USING DIGITAL HEALTH TECHNOLOGY

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AALBORG UNIVERSITY
DENMARK

ASSESSMENT OF SPATIOTEMPORAL CHANGES OF PAIN AND SENSORY PERCEPTIONS USING DIGITAL HEALTH TECHNOLOGY

PHD THESIS

by

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Dissertation submitted

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CV

Maria Galve Villa qualified as a nurse in 2001 [BSc Nursing Studies, Universidad de Zaragoza, Spain] and continued her career to qualify as a physiotherapist in 2005 [BSc Physiotherapy, Universidad Alfonso X el Sabio, Madrid, Spain]. Over her career she has gained extensive international clinical experience in a variety of settings.

In 2011 she was awarded an MSc in Neuromusculoskeletal Physiotherapy from University College Dublin, Ireland. Maria continued working in clinical practice full-time, applying her expertise in the management of musculoskeletal chronic pain conditions, and embracing the biopsychosocial model of care in the multidisciplinary healthcare setting.

In 2014, following a move to Denmark, she worked in the Pain and Headache clinic at Aarhus University Hospital, where she focused on the management of complex pain conditions, including complex regional pain syndrome. Maria has lectured in pain-related subjects in Ireland, Denmark, and continues to lecture remotely in Spain.

In 2016, Maria was accepted as a PhD Fellow at the Center for Neuroplasticity and Pain (CNAP), Aalborg University. Furthermore, she has published in international peer-reviewed journals, and has been involved in dissemination activities through congress presentations, including presenting her research at a Young Researchers Workshop at the European Pain Congress (EFIC) in Spain. Additionally, during her PhD studies Maria has been awarded “highly commended poster” and received several travel grants.

ENGLISH SUMMARY

A clinician's assessment of pain conditions relies on a patient's self-reported measures of pain and discomfort. Moreover, very little is known about the detailed changes in pain intensity and distribution between consultations. Momentary assessment of pain can mitigate recall bias and prove advantageous towards the management of pain. However, easily quantifiable measures of momentary pain are limited. The development of digital health technologies can help to overcome and improve these limitations as well as creating new opportunities to dive deeper into the mechanisms of pain.

The aim of this PhD project was to assess spatiotemporal changes of self-reported pain intensity and distribution (extent and location) in experimental and clinical pain, using state-of-the-art digital pain mapping technology. The objectives of this PhD were (1) to acquire and quantify changes of momentary pain and discomfort intensity and distribution over time, and (2) to assess the advantages, limitations, and barriers of use of the pain mapping technology.

This PhD project utilized patients with musculoskeletal chronic spinally referred pain, as well as two different models to induce pain and discomfort in healthy participants. Patients with chronic pain mapped and tracked their pain intensity and distribution over time. A well-established experimental pain model was used to induce transient acute musculoskeletal low-back pain and aimed to assess dose-response differences in evoked intensity and extent over time. A second model induced experimental discomfort and aimed to explore changes in perception.

The first study demonstrated and characterized dose-response differences in saline-evoked spatiotemporal pain intensity and distribution over time, supporting the relevance of repeated momentary pain assessment. The second study revealed previously unseen fluctuations in pain intensity and extent over a prolonged period, in patients with spinally referred pain. Additionally, results revealed patients' characteristics and barriers of use that influenced reporting compliance. Finally, the third study supported the use of modifiable animations to assist with the quantification of real-time changes in quality descriptors.

In conclusion, the current PhD thesis provides evidence of spatiotemporal changes of pain and discomfort and proposes novel digital pain metrics that may support the assessment of pain. Results from this PhD contribute to our understanding of the patients' pain experience and underscores the use of digital pain mapping in experimental and clinical research.

DANSK RESUME

En klinikers vurdering af en smertetilstand er afhængig af patientens selv-rapporterede målinger af vedkommendes smerte og ubehag. Desuden vides meget lidt om de detaljerede ændringer i smerteintensitet og fordeling mellem konsultationer. Momentan vurdering af smerte kan dæmpe erindringsbias og vise sig fordelagtig i behandlingen af smerter. Imidlertid er let kvantificerbare mål for øjeblikkelig smerte begrænset. Udviklingen af digitale sundhedsteknologier kan hjælpe med at overvinde og forbedre disse begrænsninger samt skabe nye muligheder for at dykke dybere ned i mekanismerne for smerte.

Formålet med dette ph.d.-studie var at vurdere spatiotemporale ændringer i selvrapporteret smerteintensitet og -fordeling (omfang og udbredelse) i tilstande af eksperimentel og klinisk smerte ved hjælp af avancerede digitale smertekortlægningsløsninger. Formålet med ph.d.-studiet var (1) at indhøste og kvantificere ændringer i intensiteten af momentan smerte og ubehag samt udbredelse af smerte over tid og (2) at vurdere fordele, begrænsninger og barrierer i forbindelse med brug af smertekortlægningsteknologi.

Ph.d.-studiet anvendte to forskellige modeller til at fremkalde smerte og ubehag hos raske forsøgsdeltagere samt patienter med muskuloskeletale spinale refererede smerter. Der blev anvendt en veletableret eksperimentel smertemodel til at fremkalde kortvarig akut muskuloskeletal lændesmerte med det formål at vurdere dosis-respons-forskelle i den fremkaldte intensitet og udbredelse over tid. En anden model påførte eksperimentelt ubehag med det formål at undersøge ændringer i perception.

Det første studie påviste og karakteriserede dosis-respons-forskelle i saltvandsinduceret spatiotemporal smerteintensitet og -udbredelse over tid og støttede relevansen af gentagen momentan smertemåling. Det andet studie foreslår tidligere usete udsving i smerteintensitet og udbredelse over en længerevarende periode hos patienter med refererede spinale smerter. Endvidere afslørede resultaterne patienternes karakteristika og de barrierer ved brugen, som påvirkede overholdelsen af indrapporteringen. Endelig støttede det tredje studie brugen af modificerbare animationer til at assistere med kvantificering af realtidsændringer i kopslige følelser.

Afslutningsvis påviser denne ph.d.-afhandling spatiotemporale ændringer i smerte og ubehag og afslører nye digitale smertemålesystemer, som kan understøtte vurderingen af smerte. Resultaterne bidrager til vores forståelse af patienters smerteoplevelse og retfærdiggør brug af digital smertekortlægning i eksperimentelle og kliniske forsøg.

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CHAPTER 1. INTRODUCTION

1.1 THE ASSESSMENT OF PAIN

Pain is a multidimensional and subjective sensory perception. The International Association of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage, or described in terms of such a damage"[1] (1). The subjective nature of pain leads patient-reported outcome measures (PROMS), such as intensity ratings and quality descriptors, to be the most highly recommended approach during the assessment of pain (2). However, it is a clinician's interpretation of these PROMS that can help determine a meaningful picture of the pain experience (3) to assist in the clinical decision-making process. Therefore, the accuracy of the patient-clinician communication of pain and sensory perceptions plays an essential role in the assessment of pain.

The intensity of pain and sensory perceptions can be rated using different scales, such as the Numerical Rating Scale (NRS), the Visual Analogue Scale (VAS), and the Verbal Rating Scale (VRS) (4). These intensity rating scales aim to simplify the perceived sensation to a number from 0 "no pain" to 10 "worst imaginable pain". Furthermore, these scales rely on the ability of the patients to condense the sensation perceived over a past time, to a single number (5).

Quality descriptors characterize painful sensations (e.g. throbbing, dull ache), as well as sensations provoking discomfort, namely dysesthesias (e.g. burning, electric, itch) and paraesthesias (e.g. numbness, tingling) (1,7). These quality descriptors provide valuable information during assessment (8–10) and play an important role in the understanding of mechanisms of pain (2,8,11,12). Questionnaires, such as the McGill Pain Questionnaire (MPQ) (13,14) and painDETECT (15,16), are used routinely to identify quality descriptors and assist in the differential diagnosis.

Other common PROMS capture the spatial spread of pain and discomfort using body charts. Classic pen-to-paper body charts display 2D silhouettes of a male or female body from different viewpoints (anterior, posterior, lateral right, and lateral left). Pain drawings can be a useful tool to visually represent the pain distribution (extent and location) (17) and improve the understanding of underlying pain mechanisms (18–20) in the clinical population. Pain drawings have been used to develop maps of pain distribution patterns that have become clinical diagnostic tools (21–29), such as dermatome and myotome maps (30), cervical zygapophyseal joint pain patterns (31,32), and myofascial trigger point pain patterns (33). However, pain maps may have been determined based on cross-sectional studies in healthy participants (30,31,33–36). As such, the knowledge obtained from these maps may be missing relevant information on how pain and sensory perceptions progress or

regress over time (spatiotemporal pattern).

There are few longitudinal studies outlining changes in the overall regions of pain over a sustained period (37–43). Very little is known about the detailed changes in pain intensity and distribution over time in experimental and clinical pain and whether these changes are relevant to the clinical practice. Therefore, in order to advance pain mapping, the development of novel pain metrics would be needed to more accurately quantify and capture changes in pain distribution and sensory perceptions. At an experimental level, digital pain mapping can explore the dynamic relationship between sensory perception and stimulation to gain a deeper understanding of pain mechanisms. At a clinical level, digital pain mapping can minimize pain recall biases, improve patient-clinician communication, and explore changes of pain and discomfort over time, thereby assisting the clinical decision-making process.

1.2 THE EVOLUTION OF PAIN MAPPING AND BODY CHARTS

In 1949, pain drawings were first described as a differential diagnosis tool to assess whether pain symptoms originated from organic lesions or functional nervous disorders (44). Visual inspection revealed that the pain drawing's symmetry was a key diagnostic feature and concluded that pain drawings depicted a clear visual representation of pain syndromes (44).

Simple visual inspection of pain drawings continued to be used to identify differences in pain extent and location. Pain maps that were developed from visual inspection are still in use in clinical practice (30–32,44,45). However, the methods for the mapping of pain have evolved over time (46). Pain drawings used dots, lines and crosses to visually represented the location of different pain and sensory perceptions (14,43,47). For example, a cross could represent pain, whereas a discontinued line could represent tingling. Other methods divided the body charts into different body regions, and patients filled out the area or areas of where their pain was located (48–50) and used different colors to report different quality descriptors (51). In an effort to advance the quantification of pain extent, grids made of small squares were superimposed to a body chart or pain drawings to count the number of colored squares (52,53), as an indirect measure of pain extent (pain area).

Pain drawing scoring systems were then developed as a psychological screening tool for low-back pain based on the symmetry, extent, and location of the pain (49,54–56). However, these scoring systems were not able to be validated or correlated to known psychological screening and evaluation tools (57–60). Pain drawings became digitized in the 1990s (61–64), and more advanced computerized scoring systems were developed using software assessment (65), statistical methods (66), and artificial neuronal networks (67,68) to detect patterns of pain distribution. These computerized scoring systems have shown similar sensitivity to experienced

clinicians to classify pain drawings into different diagnostic categories in patients with low-back pain (65–67). The use of pixel-count was also described as a method to quantify experimentally evoked paraesthesias (69). However, there is still no gold standard to quantify pain extent (70).

Currently in 2020, patients can indicate the pain distribution (area and location) by drawing directly onto a body chart on a mobile device (62,63,71,72). Digital pain drawings in 2D or 3D body charts have shown good correlation with pen-to-paper pain drawings (61,64,70,73–75). A clear advantage from digital pain drawings is the ability to systematically quantify the pain extent by extracting the number of pixels from the coloured areas. The use of digital pain drawings to map and track changes of pain and discomfort may assist to identify pain patterns (20,76) and reveal changes in sensory perceptions (77). A table with a summary of studies using pain drawings, including the methodological milestones, has been added at the end of this thesis (see appendix).

1.3 ECOLOGICAL MOMENTARY ASSESSMENT OF SELF-REPORTED PAIN

The accuracy of PROMS of pain relies on the patient's pain memory recall (78–82), as a patient's pain onset may occur a long time before the assessment. Factors influencing pain intensity recall include the intensity of the actual experience of pain (78,79,83), stress or distress (84,85), and pain catastrophizing (82,86,87). To reduce possible pain recall biases (exaggeration or lessening) acquiring electronic PROMS (ePROMS) in real-time as they occur (momentary) may offer more accurate information (88–90). Additionally, the acquisition of momentary pain ePROMS remotely, from the patients' own environment and context (ecological) can provide detailed relevant information (88–90). Ecological momentary assessment (EMA) of pain electronic ePROMS can provide momentary pain data repeatedly over time between clinical consultations that can be relevant for pain assessment and monitoring (88–90). Repeated momentary data collection can assist in characterizing and accurately describe the dynamic changes of the experience of pain over an extended period (89,90).

1.4 DIGITAL PAIN MAPPING

Digital health (eHealth) allows for the acquisition, storage, and sharing of digital biomarkers remotely, making eHealth the ideal methodology for the EMA of pain. Digital biomarkers are a composite of medical data collected directly by the patient (91), from the patient (92), using technology, such as digital platforms, as well as applications (apps) and wearables. Pain tracking apps, such as those for pain mapping, can acquire digital pain biomarkers, namely intensity ratings, quality descriptors, and pain drawings, remotely to reveal the spatiotemporal course of pain and discomfort, thereby gaining a broader understanding of the pain experience and

improving the accuracy of pain communication.

1.5 AIMS OF THE PHD THESIS

This chapter has introduced the interaction among PROMS, EMA, and digital pain mapping to acquire digital pain biomarkers. This interaction can lead to the identification of changes in pain distribution over prolonged periods. Digital pain mapping opens the possibility to capture momentary pain distribution and compare the accuracy of pain distribution memory recall. The need for evidence on the feasibility of digital pain mapping for the assessment of pain and sensory perceptions forms the basis of this PhD.

The overall aim of this PhD was to explore spatiotemporal changes of pain and discomfort using digital pain mapping, as well as exploring digital pain metrics to support the assessment of sensory perceptions beyond pain. Three studies were set up with specific primary aims:

1) Quantify changes of pain intensity and distribution over time, in experimentally evoked pain as well as in clinical pain, using a digital pain-mapping app. Study I determined dose-response spatiotemporal differences in experimental saline-induced low-back pain and the pain memory recall. Study II mapped and tracked pain and discomfort in patients with non-malignant referred pain from the spine for 12 weeks.

2) Assess the adjustment behavior of a modifiable animation to capture changes in experimentally evoked sensory perceptions. Study III assessed the systematic adjustment of two parameters to visually represent changes in experimental tingling sensations.

3) Determine barriers, and limitations of digital pain mapping. Studies II-III collected qualitative feedback data from the users to identify barriers, limitations, and suggestions for improvement.

1.6 OVERVIEW

This thesis is structured to provide a cohesive and logical description of the results from the three different studies. Chapter two describes the methods utilized throughout this PhD project, whereas chapters three to six present the results, as well as the existing literature. Lastly, chapters seven and eight describe the PhD project limitations, draw overall conclusions, and discuss future perspectives in digital pain mapping.

Each of the three studies used a different pain mapping technology. Table 1-1 provides an overview of the three different technologies and pain models used for

each of the studies, as well as conceptualizes the studies' relationship to assess changes in pain and discomfort over time.

Table 1-1. Overview of the three PhD studies outlining the different digital pain mapping technologies and pain models utilized.

	Pain Mapping Technology	**Pain Model**	**General Description**
Study I	Navigate Pain (Android) application	Hypertonic saline-induced low-back pain	Pain intensity ratings and digital pain drawings obtained using a tablet in the lab.
Study II	Web-based navigate Pain application	Pain and discomfort in patients with non-malignant chronic spinally referred pain	Pain intensity ratings and digital pain drawings obtained remotely using a mobile phone, tablet, or computer.
Study III	Animate Pain	Transcutaneous electrical stimulations evoking tingling sensations.	Prototype of a self-adjustable animation to capture changes in sensory perceptions.

1.7 PAPERS ASSOCIATED WITH THE DISSERTATION

The current PhD thesis includes two internationally peer-reviewed papers, and one manuscript under peer-review. The first and second paper address the first and third goal, whereas the third paper addresses the second and completes the third goal.

Study I Spatiotemporal patterns of referred pain and recall accuracy: a dose-response study. Galve Villa, M., Palsson S., T., Boudreau S.A. Scandinavian Journal of Pain (submitted)

Study II Remote digital pain mapping and tracking in patients with chronic pain. Galve Villa, M., Cid Royo A., Bjarkam R, C., Palsson S., T., Boudreau S.A. J Med Internet Res (in press). doi:10.2196/21475

Study III Modifiable motion graphics for capturing sensations. Galve Villa, M., Mørch C.D., Palsson T.S., Boudreau S.A. PLos One 2020 Feb 24;15(2): e0229139.

CHAPTER 2. EXPERIMENTAL MODELS OF PAIN AND DIGITAL PAIN MAPPING TO UNCOVER MECHANISMS OF REFERRED PAIN

Experimental models aim to mimic clinical pain and are used to explore the transition from stimulation to perception (psychometrics) to better understand the mechanisms of pain (93,94). Experimental models of pain have been used to explore patterns of evoked-pain distribution (36,95–98) by activating different nociceptors (99). Experimentally evoked muscle pain can induce centrally driven phenomena, such as referred pain (93,99,100). Referred pain is perceived at a location distally from the stimulation site (94,99).

Hypertonic saline (HS) injections are used to mimic the patterns of local and referred pain as seen in clinical conditions (94,100,101), whereas electrical stimulations (ES) are used to evoke a range of sensory perceptions (102–104). Knowledge about spatiotemporal changes of pain could improve our understanding of pain mechanisms dynamic changes. Pain studies may benefit from exploring the spatiotemporal changes in pain extent and intensity in healthy and clinical populations.

The current thesis focuses on HS and transcutaneous ES. HS intra-muscular injections are used in experimental pain research as a transitory acute muscle pain model (105), whereas transcutaneous ES are used to explore psychometric properties (106–108). Psychometric studies use a variety of stimulations and questionnaires to evoke and characterize a range of sensory perceptions. For example, differing electrical stimulation intensities can evoke different perceptions ranging from tingling to hammering (109). Changes in the intensity of the sensory perceptions are assessed using VAS or NRS. However, there are no specific PROMS to quantify changes in sensory perception.

2.1 EXPERIMENTAL MODELS OF PAIN AND OTHER SENSATIONS

2.1.1 EXPERIMENTAL MODEL OF LOW-BACK PAIN

Study I used two different doses of HS (5.8%) injections, as a model of non-specific acute referred low-back pain, to determine spatiotemporal dose-response differences in healthy participants. A single low-dose (0.5ml) or a high-dose (1.0ml) HS bolus was injected into the belly of the right gluteus medium muscle aiming to mimic soft-tissue acute low-back pain.

2.1.2 EXPERIMENTAL MODEL OF TINGLING

Study III used a range of transcutaneous ES to elicit sensory perceptions to the glabrous aspect of the index fingertip of the left hand. The protocol for electrically evoked tingling sensations consisted of 8 randomized ES intensities (2, 3, 3.5, 4, 4.5, 5, 5.5 and 6mA) with a constant number of bursts, frequency, duration of the burst and pulse width (1 burst, 250Hz, 4 seconds and 50μs, respectively), repeated three times. The ES were applied using surface electrodes (*Neuroline 700, Ambu A/S, Denmark*) placed on the proximal and distal phalanges and connected to an isolated bipolar constant current stimulator (*DS5, Digitimer Ltd, Hertfordshire, UK*). The delivery of the stimulations was controlled by custom-made software *(Mr. Kick III v. 3.0, Aalborg University*).

2.2 THE INTENSITY OF PAIN AND SENSORY PERCEPTIONS

The NRS and the VAS are well-established, validated methods to obtain a single number representing the intensity of the perceived pain experience (110,111). A modern take on the classic VAS is the electronic Color Analogue Scale (eCAS). The eCAS is a coloured line (green, yellow, red) accompanied by the words “no pain”, “moderate pain”, and “severe pain”, representing a continuum between “no pain” on the left end of the scale and “worst imaginable pain” on the right end of the scale (112,113). Electronic visual analogues scales (eVAS) for the assessment of pain have been validated in electronic format (114–116). An eNRS (study I), an eCAS (study II), and a classic NRS (study III) were used to acquire momentary intensity ratings (current), as well as the average intensity for the last 24 hours (usual). The different scales were appropriate for each of the study designs and were not intended for comparison between them.

2.3 DIGITAL PAIN MAPPING TO QUANTIFY AND QUALIFY THE PAIN EXPERIENCE

Digital pain mapping can help in the assessment of pain remotely, over a sustained period. Digital pain drawings can be assessed using image processing techniques (72) to determine novel pain distribution metrics (95,117). For example, digital pain drawings can be superimposed to create overlay images (76) for visualizing of changes in pain distribution over time (study I, see section 3.1), and identify common patterns or locations of pain (76). Additionally, digital pain mapping allows comparisons of the similarities in pain extent and distribution, between two digital pain drawings.

Digital pain mapping enables detailed patient-clinician communication, and may improve the clinician’s understanding of the patient’s pain (19). Two digital pain-mapping apps, the Navigate Pain android and web app version, were used to acquire pain intensity ratings as well as pain and discomfort extent. The pain and discomfort

extent can be quantified by extracting the number of pixels (61,72,74). This pixel count includes both, localized and referred pain and discomfort. A third digital pain-mapping app, Animate Pain, used self-adjustable animations to quantify changes in visual representations of sensory perceptions.

2.3.1 DIGITAL PAIN MAPPING APPLICATIONS

Study I used the Navigate Pain app version 0.1.9.9.3 for android (*Aalborg University, Denmark*) to capture changes in experimental saline-induced low-back pain using touch-screen technology (Fig. 2-1). A digital tablet (*Samsung Galaxy Note 10.1 2014 Edition*) displayed a high-resolution 2D male body chart in a posterior view. Participants used a stylus digital pen (S-pen) to draw the location and area of the pain on the body chart every 30 seconds until pain cessation (NRS=0). This digital drawing time-lapse captures the spatiotemporal patterns of momentary pain intensity and extent over time.

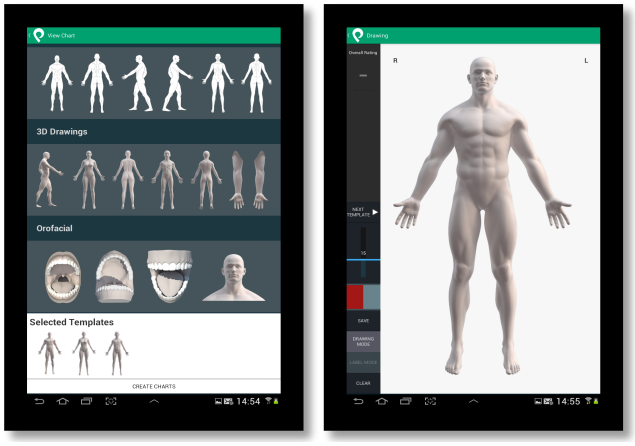

Fig. 2-1: Digital pain-mapping application to quantify the pain extent (study I). *Navigate Pain version 0.1.9.9.3 (Aalborg University, Denmark) displaying the selection of 2D body charts and the anterior view of a detailed male body chart.*

Study II used a new web-based pain-mapping app, Navigate Pain, version 2 (*Aglance Solutions, Denmark*) (Fig. 2-2), equipped with extra functions to enable remote and weekly digital pain reports. Each pain report consisted of pain drawings and pain intensity (usual and current) ratings. A computer mouse, or touch-screen technology, was used to draw the location and area of pain onto a female, or a male pseudo-3D body avatar from different viewpoints (anterior, posterior, lateral right and lateral left). Ten different color-coded discomfort quality descriptors were available to be selected (tingling, throbbing, stabbing, dull aching, numbness, itchy, electric, cold, burning, and other), as well as the general descriptor “pain”.

Additionally, a small free-text section was available for patients to comment about the pain experience.

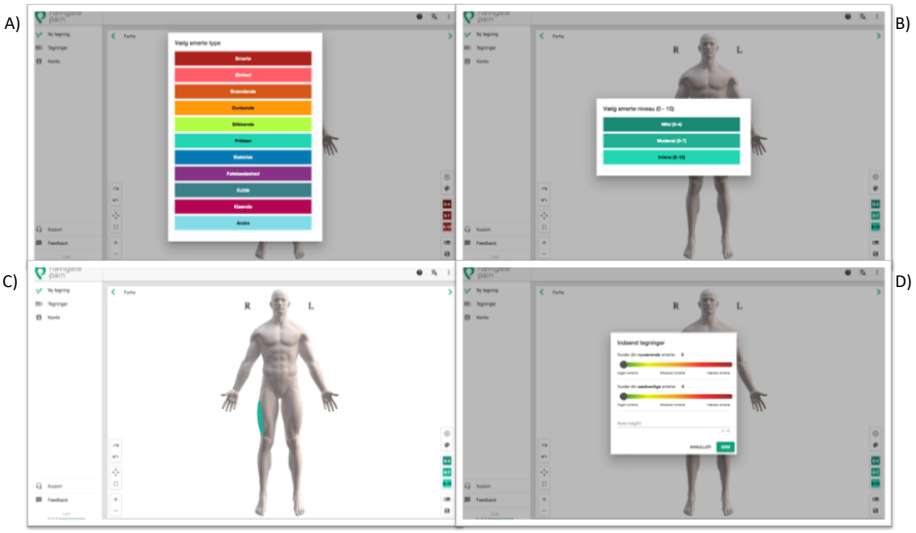

Fig. 2-2: Sequence of screenshots from the web-based digital pain-mapping application to quantify and qualify the pain experience (study II). *Navigate Pain (Aglance Solutions, Denmark) displaying the different steps required to complete a pain report. (A) Selection of the color-coded quality descriptor followed by (B) the intensity of the descriptors. (C) Completion of the digital pain drawing from different viewpoints (only anterior view displayed for illustration purposes). Steps A-C may be repeated as often as required with the different quality descriptors. (D) At the end of each pain report, patients rated their usual (average) and current pain intensity on an electronic color analogue scale. Reproduced with permission (Aglance Solutions ApS).*

2.3.2 METRICS TO QUANTIFY PAIN DISTRIBUTION.

Similarity between two pain drawings: Jaccard index

The similarity between two pain drawings can be calculated and expressed using a Jaccard similarity coefficient or Jaccard index (76). A higher Jaccard index represents a greater pixel overlap between two pain drawings and indirectly quantifies the pain distribution similarity (18,19,76). For example, the Jaccard index can be a useful tool to assess the accuracy of the experimental pain distribution recall (chapter 4). Furthermore, to assess temporal changes in pain distribution, three novel pain distribution metrics were evaluated. These pain distribution metrics can uncover changes in the pain spread, morphology (shape), and location to reveal spatiotemporal patterns of pain distribution.

Distance from origin: Vector length

The vector length measures the expansion or spread of the pain, and it is defined as the maximum distance from the injection site to the farthest-located pixel on the pain drawing. The vector length is measured in pixels and considers all the pain areas within the pain drawing.

Shape morphology: Bounding box area

Drawings of pain may differ in morphology and are, arguably, more likely to be irregularly shaped rather than perfectly circular or square. The description of irregular shapes and quantification can, therefore, be complex. A bounding box area is calculated by determining the length and width of a box that fully enclose the area of pain. The bounding box area also encloses discontinuous pain, in cases where there is more than one area of pain. The resulting length and width vectors simplify the information about the shape of the pain area or areas, enabling an easier interpretation in statistical outcomes about generalized differences or changes in pain area morphology.

Shifts in general location: Centroid

Shifts in the location of pain, for example during recall of pain, may occur. Additionally, due to the possibility of irregular morphologies in the area of reported pain, assessing changes in the location can be difficult. Therefore, calculating the centroid of the pain area can determine more detailed information about the location of the pain area whilst accounting for changes in pain area morphology. The centroid is the central point (geometric centre) of the area of pain. The centroid is determined by a X- coordinate and a Y-coordinate. These coordinates determine the centroid location horizontally and vertically, respectively.

2.3.3 VISUAL REPRESENTATIONS OF SENSORY PERCEPTIONS

Study III used state-of-the-art software to quantify changes to sensory perceptions. Animate Pain version 1.0 (*Aalborg University, Denmark*) displayed a modifiable animation on an interactive dashboard (Fig. 2-3). The dashboard displayed a high-resolution image (canvas) of the glabrous aspect of the left hand. An animation designed to represent the sensation of tingling (dots appearing and disappearing) appeared when drawing on the canvas with the computer mouse. Adjustments of two digital visual analogue scales (dVAS), located on the dashboard, modified the animation's parameters, to visually modify the density and speed of the dots from the animation in real-time.

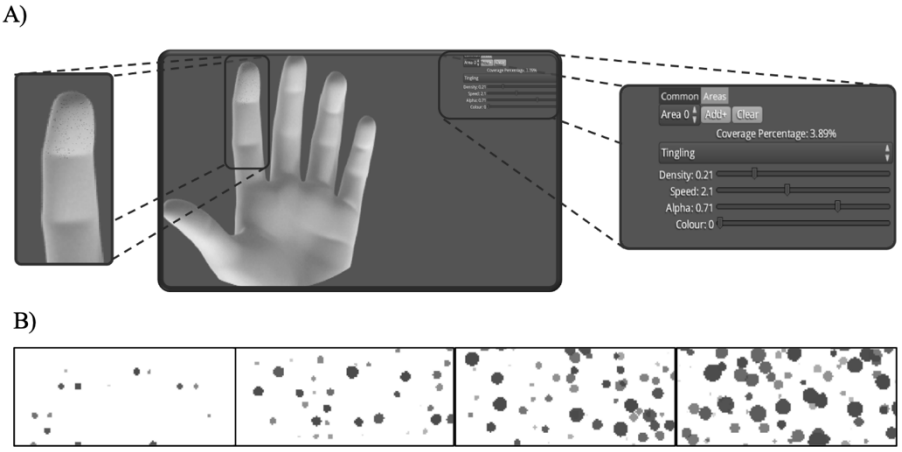

Fig. 2-3: Digital pain mapping to quantify changes in sensory perceptions. *(A) Animate Pain (Aalborg University, Denmark) dashboard displaying the digital body chart representing the glabrous aspect of the left hand. The digital Visual Analogue Scales (dVAS) modify the density and speed parameters. Images are enlarged to take a snapshot of the animation, as well as the density and speed dVAS. (B) Enlarged images of the animation, for illustration purposes, show a range of different density values from 0 (minimum), 0.2, 0.5 to 1 (maximal). Reproduced with permission (Galve Villa et al., 2020).*

2.4 QUESTIONNAIRES FOR THE ASSESSMENT OF THE PAIN EXPERIENCE

Pain catastrophizing (82,86,87) and stress (84,85) are known psychological factors that can influence, negatively or positively, the recall of pain intensity. To assess the influence of psychological factors during experimental pain, the Pain Catastrophizing Scale (PCS) and the Perceived Stress Scale (PSS) were assessed at baseline (Study I). The PCS has been used to evaluate pain-related catastrophizing thoughts as a negative anticipatory response associated with higher pain intensity (118,119). High pain catastrophizing ratings are known to positively influence the pain intensity recall (82,86,87). The PSS measures the degree of perceived stress levels by rating feelings and thoughts that may have been experienced during the previous month (120). Stress in known to influence the quantity and quality of memory formation (121–126).

Study II to assess whether catastrophizing and disability influenced intensity and extent in clinical pain. Disability was measured using the Oswestry Disability Index (ODI) and the Neck Disability Index (NDI) for patients with pain referred from the low-back and the cervical spine, respectively. The relationships among pain intensity, extent, disability (ODI/NDI) and catastrophizing scores are unclear. Some studies show no relationships (55,58,127), whereas many others show positive relationships (18,128–136).

CHAPTER 3. DIGITAL PAIN REPORTS REVEAL SPATIOTEMPORAL CHANGES IN REFERRED PAIN

Studies have shown that pain drawings completed by the patients themselves are more reliable than pain drawings completed by clinicians using the information obtained during anamnesis (137). Therefore, better patient-clinician communication of pain PROMS is an essential part of pain assessment. EMA of pain can be used to improve pain communication, minimize pain recall bias (see section 1.3), and optimize the clinical decision-making process.

Traditionally, pain intensity is assessed by either the average or the most intense (peak) pain intensity, and pain distribution is assessed by the largest area of referred pain (extent). Studies assessing the course of pain in patients with musculoskeletal chronic spinal pain have identified some patients may develop either stable or fluctuating temporal patterns of pain intensity (17,37,39,41,138,139). Furthermore, patients can show stable (localized or widespread) or variable spatiotemporal patterns of pain extent (42,140). However, these studies utilized paper-based surveys sent at intermittent time points over a prolonged period, and may, therefore, have missed the dynamic changes that could have occurred on a daily or weekly time scale.

In the research setting, knowledge of spatiotemporal changes evoked by different experimental models of pain may deepen the understanding of the mechanisms of referred pain. For example, in mustard oil evoked pain, dose-response differences have been identified, with a high dose evoking more intense peak pain than a low dose (96). However, dose-response differences in peak pain intensity have not been identified in the capsaicin pain model (97). It is unknown whether higher doses of experimentally evoked pain using different models are associated with more severe evoked pain (intensity and extent). It is also unknown whether temporal changes in evoked pain intensity are associated with changes in the evoked referred pain extent.

Studies I-II were set up to quantify spatiotemporal changes in momentary pain, as evoked in healthy participants (Study I), and in a clinical population (Study II). Study I quantified dose-response differences and recall ability in pain intensity, extent, and distribution using an experimental model of non-specific acute low-back referred pain. Study II used digital pain mapping to acquire weekly pain ePROMS remotely, in patients with chronic spinally referred pain.

3.1 DOSE-RESPONSE DIFFERENCES IN EXPERIMENTAL PAIN (STUDY I)

To assess dose-response differences, participants from study I received either a low-dose (0.5ml) or a high-dose (1.0ml) injection of HS and rated the pain intensity every 30 seconds until pain cessation. Participants were additionally randomized into drawing or non-drawing groups, resulting in a total of four groups: low-dose drawing (N=13), low-dose non-drawing (N=15), high-dose drawing (N=14), and high-dose non-drawing (N=15). Participants from both drawing groups captured the pain distribution, as well as the pain intensity every 30 seconds (see sections 2.1.1 and 2.3.1).

There were no differences in pain intensity and extent over time between the low-dose drawing and low-dose non-drawing groups ($p<0.05$), as well as the high-dose drawing and high-dose non-drawing groups ($p<0.05$). Digital momentary assessment of pain revealed dose-response differences in HS-evoked pain as assessed over time, comparing the area under the pain intensity-time curve ($z=-1.67$, $p<0.01$), as well as the for area under the pain extent-time curve ($z=-2.56$, $p<0.01$). (Fig. 3-1). However, dose-response differences were not identified at peak pain for intensity and extent. Additionally, study I showed that peak pain intensity was strongly associated with the evoked peak pain extent only when induced from a low dose ($r_s=0.77$, 35%, $p<0.01$), but not from a high dose. When combining data from the low and the high doses (pooled data) the peak pain intensity was not associated with the pain extent.

Study I showed that pain catastrophizing can be a factor influencing experimentally evoked pain intensity in heathy participants, concurring with previous studies (87). However, study I determined that pain extent may not be directly influenced by pain catastrophizing. Therefore, pain extent may be a relevant measure, in addition to pain intensity, during the pain assessment. This lack of association between pain extent and pain catastrophizing may not be applicable to the clinical population where catastrophizing scores may be higher, and the pain experience may also be more intense and prolonged.

Lei and colleagues showed a dose-response difference in HS-evoked pain over time and at peak pain (141,142). Study I showed dose response differences only over time. These contradicting results may be explained by the different HS doses and administration methods between the studies. Lei used much larger doses of HS (2.0ml and 4.8ml) administered by infusion (141,142), whereas study I (0.5ml and 1ml) administered by bolus injection. In Lei's study, the 2.0ml and 4.8ml HS-doses evoked a mean peak pain intensity (VAS) of 4.5 and 8 out of 10 (141). Study I evoked a mean peak pain intensity of 4 out of 10 for the low-dose (0.5ml), and 5 out of 10 for the and high-dose (1.0ml). The lower doses from each study differed by fourfold (0.5ml and 2.0ml) and evoked similar peak pain intensity. However, the pain duration was considerably longer (by approximately 6 minutes) for the higher

dose. On the other hand, the high dose from Lei's study evoked a considerably more intense pain intensity and pain duration (by approximately 15 minutes) than the high dose from study I. Therefore, future experimental studies could use lower doses of HS to determine dose-response differences over time, whereas higher doses could be necessary to assess dose-response differences at peak pain.

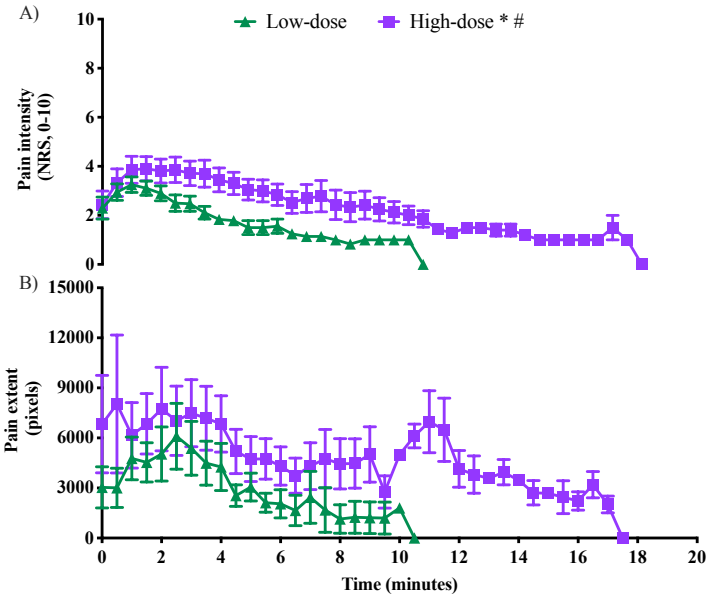

Fig. 3-1: Dose-response differences over time in pain intensity and extent immediately following (time=0) an injection of hypertonic saline (5.8%) into the right gluteus medius muscle. *A) Pain intensity ratings from for the low-dose (0.5ml) (N=27) and the high-dose (1.0ml) (N=27) drawing and non-drawing groups. B) Evoked pain area as measured in pixels for the low-dose drawing (N=13) and the high-dose-drawing (N=13) groups. A higher dose of HS evoked a longer pain duration (#) and greater area under the pain intensity-time and pain extent-time curves (*) than for the low-dose ($p<0.01$). Data are expressed as mean and standard error of the mean (SEM).*

Novel findings of dose-response spatiotemporal differences were shown as measured by pain distribution metrics (see section 2.3.1). These metrics showed a greater overall spread in pain, as reflected by the size of the bounding box area, and a larger spread laterally towards the hip (X coordinate centroid) over time for the 1.0ml than for the 0.5ml dose. However, the distance from the injection site (vector length) was similar between doses. Therefore, HS evokes a larger spread (morphology shape) in pain by increasing the dose. These pain distribution metrics were not able to identify intra-dose spatiotemporal patterns of pain distribution for the 0.5ml, or the 1.0 ml dose. The lack of clear patterns of pain distribution for each of the HS doses may be explained by a large variability in pain extent and the moderate pain intensity evoked (Fig. 3-1). Future experimental studies aiming to

identify spatiotemporal patterns of pain distribution may need to use a high dose of HS to evoke more intense and extensive pain.

3.2 FLUCTUATIONS IN CLINICAL PAIN INTENSITY AND EXTENT (STUDY II)

Patients with chronic pain (N=78) were requested to submit weekly digital pain reports to map, track, and quantify changes of pain intensity and distribution over 3-months (143). Sixty-five patients submitted, at least, one pain report over a 12-week period. Digital mapping and tracking of patients with non-malignant (somatic and neuropathic) chronic spinally referred pain provided detailed information about the changes in intensity (usual and current) and extent of pain and discomfort over time (see sections 2.2 and 2.3). Fluctuations in the pain intensity (usual $\chi^2(11) = 145.34$, $p < 0.001$; current $\chi^2(11) = 105.66$, $p < 0.001$), and pain and discomfort extent ($\chi^2(11) = 48.74$, $p < 0.001$), over 12 weeks were revealed (Fig. 3-2).

Data obtained from the weekly digital pain reports were pooled to assess whether the weekly fluctuations were also identified on a monthly interval. Results showed similar pain extent and intensity ratings when assessed monthly ($p>0.05$). These results suggest that frequent assessment can capture fluctuations of pain, supporting the use of digital pain mapping for the acquisition of digital pain biomarkers.

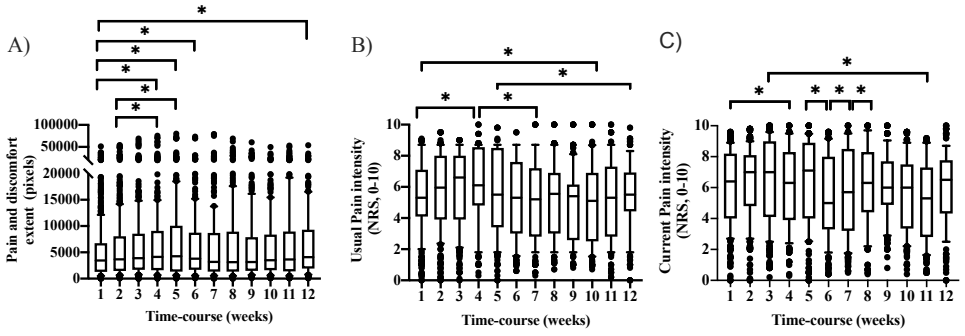

Fig. 3-2. Fluctuations in pain and discomfort extent and intensity, over a 12-week period, in patients with non-malignant chronic spinally referred pain (N=65). *Graphs showing fluctuations of pain area (A), usual (B) and current (C) pain intensity ratings over the 12-week period. The box and whiskers graphic show the median of the overall pain area and intensity in the different weeks. The whiskers are drawn down to the 10th percentile and up to the 90th. Points below and above the whiskers are drawn as individual dots. Reproduced with permission (Galve Villa et al. 2020).*

Observation of the individual pain drawings highlighted that patients reporting a larger pain extent pain showed a greater pain extent variability, as opposed to patients reporting a lesser pain extent that tended to remain stable over time (r_s=0.25 (3%), p<0.001) (Fig. 3-3).

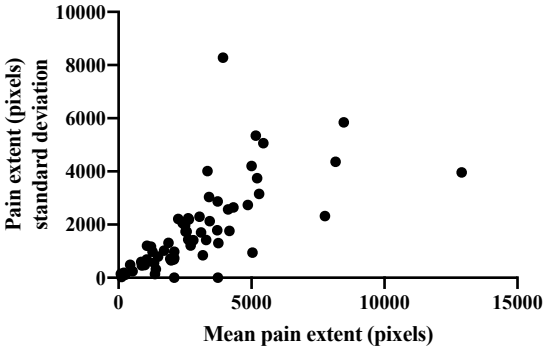

Fig. 3-3. The larger the mean pain extent, the more likely it is that the pain extent will vary over time. *The graphical relationship between the mean and standard deviation for the overall pain extent could explain the group pain fluctuations in patients with non-malignant chronic spinally referred pain.*

3.2.1 THE INFLUENCE OF PAIN CATASTROPHIZING AND DISABILITY ON CLINICAL PAIN

At baseline, patients from study II were asked to choose their primary pain site (cervical spine or low-back pain) to explore differences in the quality descriptors selection, as well as disability and pain catastrophizing scores (see section 2.4). A multiple linear regression determined that current pain intensity ratings, disability, and pain catastrophizing scores predicted the pain extent in patients with low-back pain as their primary pain site ($F(3,33)=5.28$, $p<0.05$, $R^2=32\%$). Only the pain intensity added statistical significance to the prediction ($p>0.05$). However, these same variables did not predict the pain extent in patients with cervical pain as their primary site.

A weak correlation between pain intensity (usual and current) and extent was found ($r_s=0.23$ and 0.25, respectively, $R^2=3\%$, $P<.001$), suggesting that patients with a larger pain extent may also have more intense pain, but it does not explain the intensity variance. These results are similar to previous studies (127,144–146), suggesting that the assessment of changes in pain extent may be as relevant as the assessment of changes in pain intensity for the management of pain. This means, in neurophysiology terms, that more intense pain may have activated the latent collateral synaptic connections from the dorsal horn, increasing the extent of afferent information (147). This larger afferent information may be perceived as a larger area of pain extent (referred pain).

Patients from study II did not report pain catastrophizing scores high enough to be considered “catastrophizer thinkers” (scores above 30 out of 52), but they did report high levels of disability. This was an unexpected finding as higher pain

catastrophizing scores are generally associated with a higher level of disability (118,148–150). However, it remains unclear how disability and catastrophizing scores influence pain intensity and pain extent. Our study could not show any associations between baseline pain catastrophizing and disability scores with pain intensity and extent ($p>0.5$), in line with previous findings in similar populations (55,58,127). However, positive associations for total extent and disability scores (18,129–133), as well as pain catastrophizing (128,129,134–136) have been shown in patients with chronic musculoskeletal pain. Study II assessed pain catastrophizing and disability only at baseline. Therefore, it is possible that variations of catastrophizing and disability scores over time could be associated with variations of pain intensity and extent.

3.3 CONSISTENCY OF PAIN AND DISCOMFORT QUALITY DESCRIPTORS (STUDY II)

The weekly digital pain reports included quality descriptors, as selected from a list of eleven possible words (see section 2.3.1). Contrary to the weekly fluctuations seen in pain intensity and extent, the selection of pain quality descriptors remained stable over time as a group ($p>0.05$) (Fig. 3-4).

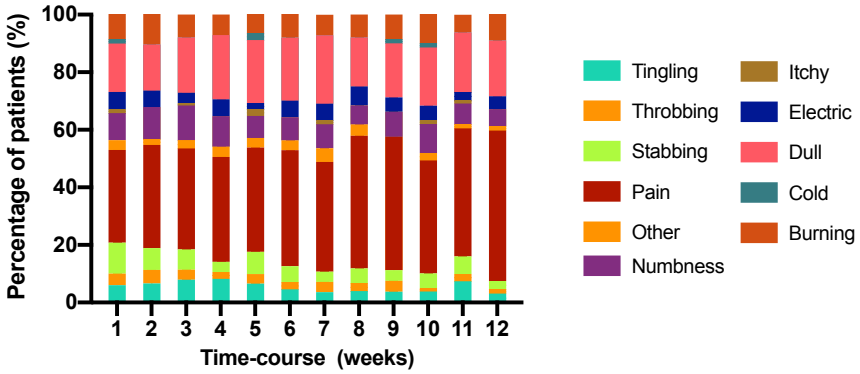

Fig. 3-4: Consistency of pain and discomfort quality descriptor selection spanning 12 weeks in patients with non-malignant chronic spinally referred pain*. A quality descriptor was accounted for only once a week, for each of the patients, independently of the submitted number of pain reports with that same quality. "Pain" and "dull aching" were the most frequently selected descriptors, followed by "numbness", "burning", and "stabbing". "Itchy", "cold", and the general descriptor "other" were the least selected. Reproduced with permission (Galve Villa et al., 2020).*

Pain and dull aching were selected by 55-76% of the patients and was similar based on gender and primary pain site. Interestingly, the males from the cervical pain cohort did not use the quality descriptors cold, itchy, or other. Gender differences have been identified in pain perception for chronic pain conditions, but generally focused on pain intensity and severity (151–156), with few studies exploring gender

differences in quality descriptors. Similarly to our study, Jensen et al (151) found no gender differences among different chronic pain conditions, including back pain and fibromyalgia. However, gender differences in the selection of quality descriptors for shoulder pain have been found using a list with 36 Chinese quality descriptors (155). This lack of differences in gender and primary pain site, supports the notion that the pain experience is driven by underlying mechanisms (157–160), rather than pain location or diagnosis.

3.4 DIGITAL PAIN MAPPING TO CAPTURE THE CONTEXT OF PAIN

Upon submitting a pain mapping report, a comment section was available for patients to add additional information not captured by the pain reports but still important for the patient (161). Eight patients (10%) voluntarily submitted 225 free-text comments with the pain reports. Six female patients with low-back pain submitted 83% (N=187) of these comments, whereas two male patients with neck pain wrote the remaining 17% (N=36) of comments. Although the comments were voluntary, a review showed that patients utilized this section to rationalize their pain reports. These comments were categorized into two themes: justification and further description. Justification of the pain experienced included physical and psychological factors that appeared to increase or improve the pain. Description of the pain experienced included other symptoms and explanations not captured within the pain drawings (Table 3-2).

Qualitative data obtained from the pain report comments gave some context to the weekly pain fluctuations. The results suggest that (i) some patients are aware of activities or life events that influence their pain, such as social gatherings or physically demanding activities, (ii) that the full impact of pain was not fully captured by the pain reports, and (iii) that perhaps more quality descriptors were necessary. Knowledge and awareness of the activities that influence pain could lead to better understanding of the pain condition, as well as to optimize pain management (157).

Table 3-2. Selection of comments extracted from the patients' pain reports divided into themes.

Justification of the pain experienced	Description of the pain experienced
-Amitriptyline increased to 10mg in the evening. -On holidays, poor bed. -Weather unstable. Cool and humid. -Daughter had celebrations yesterday. -Packing for holidays. Stressed out. -Walked a lot. 14 km in 2 days. -Relaxing completely. Inactive! -Beautiful weather. Relaxed all day. -Attended psychologist. It helped. -Vacuumed and watered the garden. -Painted using a ladder for the last 3 days. - Back at work after holidays. It feels worse. - My back feels very tired. I had guests yesterday. -After physical activity and wrong movement.	-Alternated between severe tenderness and pain. -Feeling tired all day. -Feeling very tired and inflamed. -Cramps from the knees and upwards. -I don't feel my legs sometimes. -Diffuse tenderness. -Provoked by the extension of the leg. -Acute, intense pain when lying down. -Feels mostly stiff. -Worst on the left side, down the leg. -Constant tenderness. -Pressure, numbness, deep tenderness. -Radiating towards the left hand. Headache 4 times.

3.5 SUMMARY OF THE MAIN FINDINGS FROM STUDIES I-II (MOMENTARY PAIN ASSESSMENT)

Studies I and II used a pain-mapping app to track experimental and clinical pain, respectively, over a prolonged period. The findings from studies I and II revealed that:

• The dose-response spatiotemporal differences in HS evoked-pain are consistent with the limited literature available. However, dose-response similarities found at peak pain contradict previous findings.

• There is no association between experimental peak pain intensity and extent in HS evoked pain.

• Novel pain distribution metrics (i.e. bounding box area, centroid, vector length) were identified as a useful tool to determine spatiotemporal patterns of experimental pain.

• In patients with non-malignant chronic spinally referred pain, fluctuations in weekly pain intensity and extent were evident, as captured remotely. However, the selection of pain and discomfort quality descriptors remained consistent over time.

• In patients with non-malignant chronic spinally referred pain, there is a weak association between pain intensity ratings and pain extent.

• Digital pain-mapping apps can be a useful communication tool to acquire detailed pain reports remotely, repeatedly over time. However, awareness of the patients' context affecting the fluctuations in pain intensity and extent may be key in clinical pain management.

CHAPTER 4. ASSESSING THE RECALL ACCURACY OF PAIN REPORTS USING DIGITAL PAIN MAPPING

Pain extent and distribution have been used to guide the differential diagnosis of somatic referred low-back pain and radicular low-back pain (162–164). Patterns of pain above or below the knee can suggest somatic or radicular pain, respectively, leading towards different pain management.

Clinician's depend on recalled pain PROMS as, likely, there is a time delay from the pain onset until the clinical assessment. Pain intensity recall can be affected by psychological (e.g. pain catastrophizing thoughts, perceived stress), social, and cultural factors in the clinical population (128,165–169). Additionally, pain catastrophizing is also a factor known to influence the recall of pain intensity in experimental pain (87). The relevance of the momentary assessment of pain extent, determined in the current PhD thesis, raises questions concerning the accuracy of the pain extent recall.

There are no studies currently exploring the recall accuracy of pain extent and distribution, as well as factors that may influence the recall accuracy. Furthermore, it is unknown whether the reporting of momentary pain (by way of digital pain drawings) influences the accuracy of the pain extent and distribution recall at a later time. Therefore, a goal of study I was to assess the influence of momentary pain reporting on the accuracy of pain recalled 7-days later. To our knowledge, study I explores for the first time the recall accuracy of pain distribution and extent using digital pain mapping seven days after inducing experimental low-back pain.

4.1 THE ACCURACY OF PAIN INTENSITY AND DISTRIBUTION RECALL (STUDY I)

Participants (N=57) were randomized at baseline into either a low-dose drawing (N=13), low-dose non-drawing (N=15), high-dose drawing (N=14), or high-dose non-drawing (N=15) group (see section 3.1). Seven days later, all the participants were invited to recall the peak pain intensity and complete a pain drawing representing the largest pain distribution evoked by the injection at baseline. Intensity ratings and pain drawings between the baseline and recall sessions were compared to assess recall accuracy among the four groups.

The pain intensity accuracy was assessed by calculating the intensity recall error. The accuracy of the pain distribution recall was assessed by calculating the extent (pixels) of the recall error, the Jaccard index, the homogeneity of variance, and comparing the pain distribution metrics. Results showed no differences in intensity,

extent, and distribution. Additionally, results showed a low recall error for intensity and extent, indicating a good recall accuracy in intensity, extent, and distribution among the four groups. Therefore, the continuous drawing task did not influence the accuracy of the pain distribution recall. Similar pain intensity recall accuracy results have been shown in cold-pressure test evoked-pain (87). These results suggest that a seven-day period does not affect the pain memory recall accuracy in healthy participants following a single pain event.

4.2 FACTORS THAT MAY INFLUENCE MOMENTARY AND RECALL EXPERIMENTAL PAIN

Even though there was a similar peak pain intensity and extent between two different doses of HS, study I showed that peak pain intensity was strongly associated with the evoked peak pain extent following a low dose of HS, but not a high dose (see section 3.1). These dose-response differences suggest that (i) the experimentally evoked pain intensity may not be associated with the extent of referred pain following HS injections, or (ii) the high dose may have reached a ceiling-effect in the evoked extent.

Pooled data revealed that momentary peak pain intensity was the only factor that may have influenced the pain extent recall (r_s=0.60, R^2=43%, p<0.01), similar to the association found between intensity and extent in clinical pain (study II). Additionally, pain catastrophizing was asserted as a factor associated with the perception of momentary peak pain (r_s=0.54, R^2=14%, p<0.01), and recalled peak pain intensity (r_s=0.46, R^2=22%, p<0.01), in experimentally evoked pain, as shown in other studies (87,170). Furthermore, pain catastrophizing is associated with perceived stress ratings (r_s=0.36, R^2=14%, p<0.01), in healthy participants.

4.3 SUMMARY OF THE MAIN FINDINGS FROM STUDY I (PAIN RECALL ACCURACY)

Study I assessed the influence of a continuous pain drawing task on the accuracy of the pain distribution memory recall. The findings from study I revealed that:

- Participants had a good pain intensity, extent, and distribution recall accuracy in response to a non-specific acute soft tissue low-back pain model seven days later. Continuous pain drawings did not influence the pain memory recall.

- Pain catastrophizing is re-affirmed as a psychological factor influencing momentary and recall intensity in experimental pain.

- Experimentally evoked peak pain extent is associated with peak pain intensity but not with pain catastrophizing. Therefore, pain extent may be less susceptible to factors influencing pain PROMS in healthy participants.

CHAPTER 5. IN-DEPTH ANALYSIS OF THE CLINICAL USE OF DIGITAL PAIN MAPPING

The feasibility of using digital pain mapping for tracking momentary clinical pain intensity and distribution remotely, relies on the patients' usability, ease of use (171,172), and reporting compliance (173). To facilitate the digital pain-mapping compliance the app needs to be easy to use (174) to create a seamless transition from pain and discomfort perception to communication via a digital report. Additionally, users (patients and clinicians) need to feel that submitting pain reports adds value by enhancing their communications experience (175,176), thus is beneficial and meaningful for them. Meaningfulness may be the key to understand the users, motivation to adopt the technology and, subsequently, achieve a successful implementation in healthcare settings (177). Study II revealed good usability and acceptance scores, as rated using a System Usability Scale (SUS) and a modified Technology Acceptance Model (mTAM) electronic questionnaires. However, reporting compliance ratings exposed differences between users' characteristics. Therefore, exploring the barriers of use that lead to low compliance rates may be relevant to maximize the advantages that digital pain mapping can bring to the clinical assessment of pain.

In chapter 3, we reviewed how digital pain mapping can reveal spatiotemporal changes in pain that would otherwise go unseen. These changes can provide timely, detailed information to support clinical decision-making. Furthermore, digital pain mapping allows for further development of pain mapping metrics and exploration of the value for assessing and treating clinical pain.

5.1 DIGITAL PAIN-MAPPING REPORTING COMPLIANCE. (STUDY II)

Patients (N= 78) were asked to complete one pain report weekly during a 12-week period. Patients were aware that the pain drawings were not going to be reviewed by a clinician. However, they were offered a summary of their pain reports at any time during the study. Once a patient registered with the pain-mapping app, a weekly reminder e-mail was set up. At the 6-week mid-point, patients were retrospectively divided into those who had submitted the pain reports weekly (regular users, N=35) and those who submitted pain reports less frequently (non-regular users, N=27).

The total number of submitted pain reports was 3,863. A total of 65 patients (compliance rate at study start=83%) submitted a total of 518 pain reports during the first week. A drop-out rate of 32% (N=21) of patients by the end of the study resulted in a retention rate (number of participants) of 56% at the 12-week point (fig.

5-1), determining an average patient retention rate of 56%. The number of pain reports submitted (reporting compliance) was reduced from 518 pain reports during the first week to 212 at 12 weeks, representing a compliance rate reduction of 60%. The largest drop in the compliance rate occurred during the second week, where the retention rate decreased by 22% (N=14). It is possible that this initially large drop in retention and, subsequently, compliance was due to a loss of enthusiasm and lack of perceived benefit. The retention and compliance rates steadily decreased during the first 6 weeks, where the retention rate dropped by 25%, from 65 to 49 patients, and the compliance rate dropped by 52%, from 518 to 251 pain drawings. Only one patient requested a summary, suggesting that compliance did not hinge on this offer. Studies using EMA to track pain intensity in clinical settings (88,90,178) reported a compliance rate of 85%, similar to our 83% compliance rate at week-1. Additionally, a meta-analysis of EMA studies (88) identified an average compliance rate decline of 2% per week of data collection. A hypothetical 2% weekly decline from the 83% compliance rate at week-1, would result in a week-12 compliance rate of 61%, similar to the actual end-of-study rate of 59%. Therefore, we can conclude the retention and the compliance rates from this study may not have differed if the pain reports would have been used clinically.

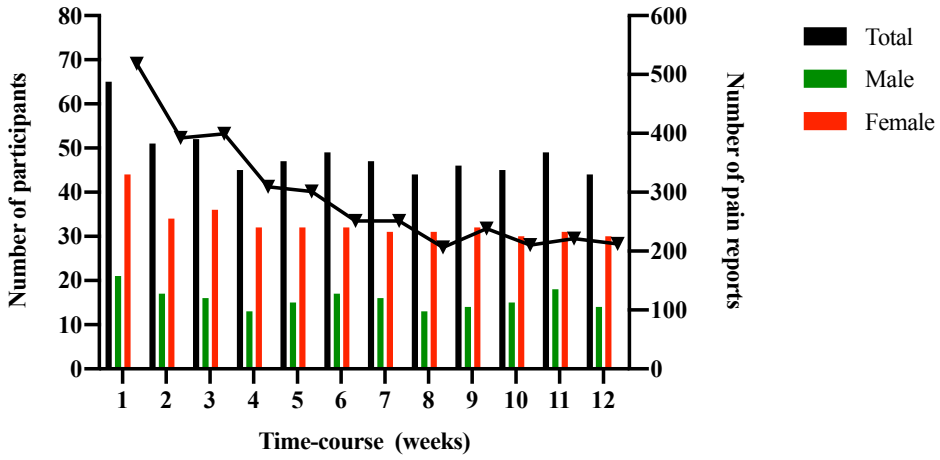

Fig. 5-1. Number of active participants and submitted pain reports during the 12-week study period. *There was an immediate drop in the number of patients (retention) using the digital pain-mapping app following the initial recruitment (left). Subsequently, the retention stabilized until the end of the study. There was a small reduction in retention during some specific weeks, which may coincide with the participants' peak holiday period. Similarly, there was a gradual reduction in the number of submitted pain reports (reporting compliance) for the first six weeks of the study (mid-point), and it subsequently reached plateau for the remainder of the study (right).*

A range of working strategies to improve or maintain patient motivation and engagement during EMA of pain studies include the use of monetary incentives,

participant-researcher direct interaction, limiting the duration of the data collection period, and the creation of a "rapid-feedback" in relation to the individual data collection (88). "Rapid feedback" in digital pain mapping could be a simple comparison between the current and a past pain report for a quick visualization on the pain progress.

In view of the steady decline in reporting compliance at week-6, a participant-researcher direct interaction strategy was developed, where each patient received a hand-written thank you card. The aim of the card was to thank the patients for participating in the study, acknowledging their time and effort during the 12-weeks, and the importance of their contribution to the study success. Subsequently, the reporting compliance rate remained stable until the end of the study. The motivational effect from the card may be considered as positive reinforcement conditioning. Positive reinforcement rewards behavior considered good, to encourage the good behavior to continue. In this case, the good behavior was submitting weekly pain reports and the reward was thanking the participants and showing our appreciation with compliments and positive statements in an individualized manner. Although it cannot be concluded that the thank you card had an effect in the stable compliance rate for the remaining of the study, the consistent retention rate should be considered as an additional strategy to maintain reporting compliance.

5.1.1 FACTORS INFLUENCING REPORTING COMPLIANCE

To identify factors influencing compliance using digital pain mapping, differences in recruitment strategies, age, gender, as well as pain intensity and extent were examined. In study II, patients were recruited by collaborating clinicians from a hospital or through social media platforms. Sixty-two percent (N=57) of the participants were recruited online. Baseline disability (ODI/NDI) and pain catastrophizing (PCS) scores were similar for both recruitment strategies ($p>0.05$). However, patients recruited from the online strategy were younger (48.7±12.13) than the patients recruited from the traditional in-house strategy (59.19±13.38, $p<.001$). Participants recruited by the two approaches may differ in their character, as the online recruits need to pro-actively get in contact with the researchers, as opposed to being invited to participate.

One of the most defining differences between regular users (RU) and non-regular users (NRU) was the age difference. The RU were approximately 7 years younger than NRU (RU=48.7±11.19 years; NRU=55.80±15.30 years, $p<.001$). This age difference may have been associated with users' respective recruitment strategy, with 80% of the RU recruited online, as compared to 56% of the NRU ($p<0.01$). A meta-analysis by Ono et al. (88) identified older patients (age≥60 years) as having a better reporting compliance in EMA studies for chronic pain patients using an app or

a diary to collect momentary pain intensity ratings over time. The mean age (48.70±13.08 years) of the participants from the meta-analysis (88) was similar to the mean age of the participants from study II (51.80±13.50 years), suggesting that the relevance of age in the compliance rate may reflect the data collection method rather than the EMA methodology.

All participants were invited to complete electronic questionnaires to explore usability and acceptance of the pain-mapping app, with an overall response rate of 88% (N=57). Differences were identified in the device (e.g. mobile, laptop) and the pathway used to access the platform between the RU (N=33) and NRU (N=24) (Fig. 5-2). Additionally, 82% of the NRU relied on the weekly reminders to submit pain reports, as compared to 39% of the RU. It is possible that easy and regular access to a computer or laptop, for example at work, may influence the reporting compliance, as patients reported that drawing their pain on a computer or laptop, rather than a mobile phone, was easier (see section 5.3). This would be consistent with the RU using the direct URL (uniform resource locator) to access the app.

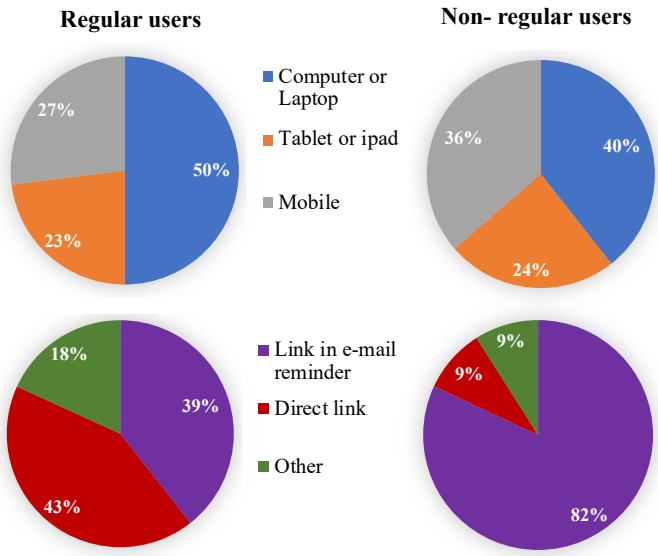

Figure 5-2. Differences in digital device use and access path to the digital pain-mapping app. *Fifty percent (N=17) of the regular users accessed the pain-mapping app from their computer or laptop, as compared with 40% (N=10) of the non-regular users. Regular users did not rely on the weekly reminder to submit the pain reports as much as the non-regular users. URL: uniform resource locator.*

RU and NRU had similar scores in the SUS and mTAM questionnaires ($p>0.05$). However, differences in the pain experience provided insights into the compliance ratings for digital pain mapping. RU reported a larger pain extent (4063 pixels IQR

8073.5) than NRU (3221 pixels IQR 4925, $p<0.01$). Furthermore, pain intensity was lower for RU (5.8± 2.73) than the NRU (6.30 ± 2.3, $p>0.01$). These results show that pain extent, rather than pain intensity, as well as age, are factors influencing the reporting compliance rate. These results suggest, that the pain-mapping app was likely viewed as a useful tool to communicate pain extent.

A logistic regression was unable to predict the probability of better reporting compliance in relation to the severity of the pain symptoms, including current pain intensity ratings, extent, and disability (ODI/NDI) scores at baseline. Further analysis revealed that differences identified between RU and NRU in pain intensity and extent, may not be clinically relevant. The eCAS intensity ratings difference of 0.3±0.5 points ($p<0.01$), out of 10, is less than the recommended 2 points or more, out of 10, to be considered clinically significant (179). Visual assessment of digital pain drawings representing the mean number of pixels for the RU and the NRU, suggest that statistical differences were unlikely to be clinically relevant. Fig. 5-3 shows that clinical decisions cannot rely solely on the pixels accounting for the pain extent. Distribution also has an influence and needs to be considered, simultaneously with extent, during the clinical decision-making process. To date, it is unclear how much the pixel count needs to change to achieve clinical significance. Additionally, the relevance of the pain extent and distribution may differ based on the location, as shown in fig. 5-3. Therefore, digital body mapping can provide relevant detailed information about extent, distribution, and location to assist the clinical decision-making process.

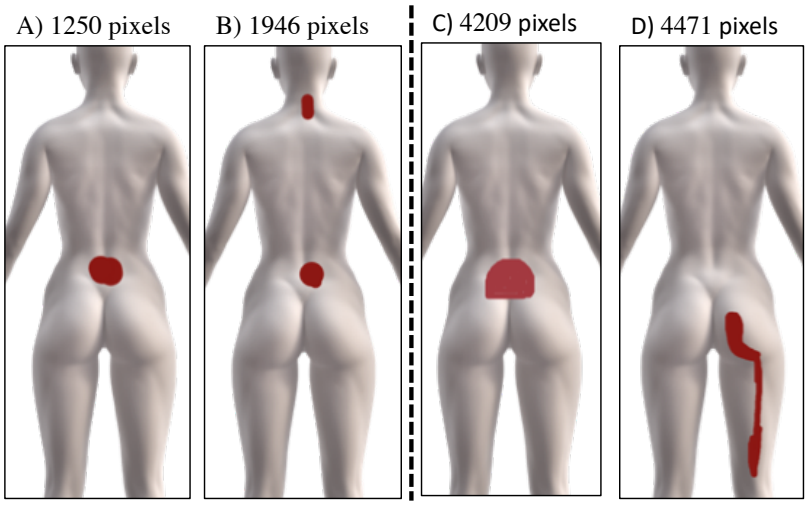

Fig. 5-3. Examples of four (A-D) pain drawings showing how pain extent and distribution should be simultaneously considered in research and clinical settings. *The pain extent, as measured by the number of pixels, in figures A and B, as well as in figures C and D may not be statistically different. However, the varying pain distribution among figures can have different clinical relevance.*

5.2 BARRIERS OF USE FOR DIGITAL PAIN MAPPING

The previous section described the factors influencing the compliance rates for the digital pain-mapping app. Exploring barriers of use may also reveal valuable information to develop feasible strategies to improve the compliance rate in prospective pain mapping studies. Furthermore, these strategies may also be utilized in the clinical setting to improve compliance in symptom tracking and monitoring.

Patients completed a Navigate Pain-specific electronic questionnaire at the mid- and endpoints of the study. Approximately 70% of the RU (N=24) and 60% of the NRU (N=15) rated the pain-mapping app, as easy, or very easy to use in general. Subsequently, patients were asked what made the pain-mapping app easy or difficult to use. Representative responses are summarized and transcribed from Danish to English in table 5-2. Additionally, to understand the reason behind the poor compliance, the NRU were asked why they did not submit pain reports regularly. None of the NRU selected the options "I'm not interested any more" or "I did not have time", as the reason for poor reporting compliance. Forty-five percent (N=10) selected "forgetfulness", whereas 13% (N=3) selected "too much" (N=2), or "no pain" (N=1) as reasons for poor compliance. The remaining 41% (N=9) selected "other". Therefore, understanding the patients' motivation to complete pain reports may be useful to optimize the compliance rate. This suggests, further studies are necessary to understand compliance behavior.

Table 5-2. Selected comments describing the digital pain-mapping app as easy or difficulty to use, from patients with non-malignant chronic spinally referred pain (N=57).

Easy to use	**Difficult to use**
-Reasonably easy after using it a few times. -Easy to handle. -There is a good user guide. -Nice. Reasonably straight forward. -It is very clear and easy. A child would almost be able to use it. -It is intuitive. -You can draw the pain with the mouse. -Good educational tool. -It is easy to erase if you draw incorrectly. -You can draw directly on the picture.	-A little difficult to draw. -Difficult to understand the symbols. -Hard to get started. -Hard to draw accurately. -Seems to be missing some descriptors such as electric shock. -The save button is not easy to find. -Too small to draw on a mobile phone. -The symbols make no sense. -Difficulty using the mouse to draw the pain.

Barriers of use related to technical aspects where identified. These technical difficulties included difficulties to register and log in, unable to receive reminders, and unable to zoom over a desired body region. Furthermore, the cause of 92% (N=12) of the dropouts were technical difficulties with the login process into the pain-mapping app. Some of these technical difficulties were due to using outdated web-browsers, as the pain mapping software is web-based and not a native mobile

app. This means the user logs on to a web page to perform pain mapping, not by opening an app installed on a mobile phone. A web app requires no personal information from the users and updates can occur more quickly. However, compatibility and display issues can pose as limitations. An in-depth comparison of advantages and disadvantages of the mobile versus web-apps are beyond the scope of the thesis; however, interpretations of the results should consider that some dropouts were due to technical barriers and with further development can be overcome.

Three factors were identified to have influenced the digital pain-mapping reporting compliance: (1) technology literacy, described as familiarity with the digital device used and navigation of websites, (2) the patient's motivation to use the pain-mapping app, and (3) a deep understanding of the user journey map from log in to the submission of the pain reports. Therefore, clinicians and researchers alike, need to consider the patients digital technology literacy when using digital health solutions. Additionally, digital health developers need to consider the users digital journey map to maximize compliance rates.

In this section, we have discussed the factors influencing and the barriers of use of the pain-mapping app. However, despite all patients receiving the same information and instructions on how to complete the digital pain drawings, an unexpected amount of differing drawing styles or behaviours emerged within the pain drawings data set. It remains unclear whether these differing drawing styles represent a poor drawing technique or skills, result from a misinterpretation or misunderstanding of the drawing instructions, or represent an individual's interpretation of the pain experience (fig. 5-4). Therefore, it is essential to deliver standardized and clear instructions of use to minimize communication barriers due to misinterpretations and, misunderstandings (46).

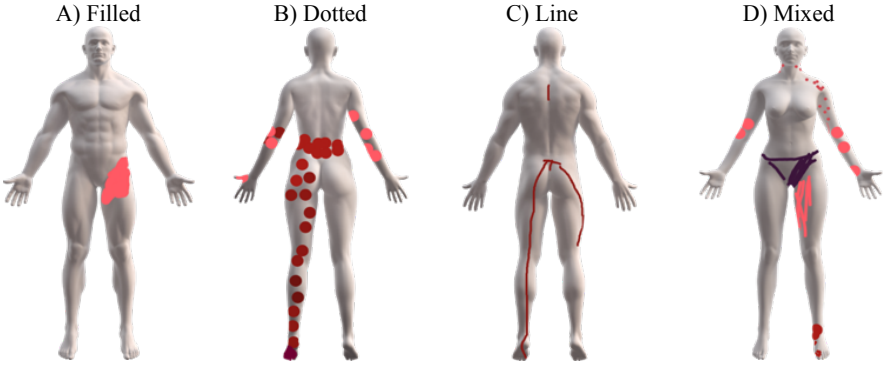

Fig. 5-4. Illustrative representation of different pain drawing techniques*. All patients were asked to complete pain drawings by filling out the area of pain. Patients expressed their pain by colouring a defined body location by using (A) different size dots spread over the body (B), fine lines, or (C) a combination of dots and lines (D).*

5.3 A PATIENT'S PERSPECTIVE: SUGGESTIONS FOR IMPROVEMENT AND CLINICAL USE:

At the end of the data collection period (week 12), all RU and NRU (N=62) were asked to complete an electronic user-experience (UX) questionnaire about using the pain-mapping app. Specifically, patients were asked to provide suggestions on how the app could be improved, how to reduce forgetfulness to improve compliance, and their opinion regarding the clinical usefulness of the digital pain reports. Similar to the usability and acceptance questionnaires acquired mid-way, patients received a small monetary compensation upon completion of the UX questionnaire. However, only 23% (N=14) responded. Table 5-1 summarizes the feedback. The suggested improvements relate to technical issues and education about pain self-management. The technical issues were forwarded to the pain-mapping app developers to improve the UX and user interface. The suggested pain self-management improvements including automatic comparison between consecutive pain drawings, and identification of pain distribution patterns to suggest potential causes and treatment options. These suggestions would correspond with the "rapid feedback" strategy to improve or maintain reporting compliance (see section 5.1.), as well as the patients desire to self-manage their pain. Additionally, this feedback identified a discrepancy between patients who want less quality descriptors available, and those who want more descriptors, as well as emotional descriptors.

To reduce the forgetfulness described as a reason for poor compliance in the NRU, suggestions consisted of notification messages and a reward point system. The reward system would be similar to the concept of "rapid-feedback" suggested by Ono et al. (88) to improve compliance. For example, using positive reinforcement strategies, this reward system could be a scale showing how good the individual's compliance is in relation to a group or the award of "digital badges" for achieving pre-set compliance milestones. Lastly, the majority of patients considered pain mapping as a useful tool to track and communicate their pain with healthcare professionals. However, the users expressed concerns about the limited time available during consultation, and the use of clinical time that would be needed to review the pain drawings.

Table 5-1. Selected comments describing improvement, motivation techniques, and perceived clinical usefulness of the digital pain-mapping app in patients with non-malignant chronic spinally referred pain (N=14).

Suggested improvements	Suggestions to minimize forgetfulness	Perceived clinical usefulness
-Information about the symptoms and pan relief options. -Improve the pain intensity scales. -An automatic comparison between pain drawings. -More pain descriptors. -Have fewer words to describe pain. Now it is too confusing. -Add words to describe emotional and physical feelings, such as fatigue. -Options to modify the saved pain drawings. -Provide possible causes for the changes in pain to learn about your pain. -Improve the zoom feature.	-Make it a downloadable app for ease of access and set up notifications. -Maybe something with a point system. -Send reminders every day until answered. -Send a SMS. -Perhaps, if the drawings were used for treatment, it would be better.	-Yes. Clinicians only ask about the pain I have at that time and not overall. -No, but it helps me to communicate my pain. -Yes, it is easier than a pain diary. -Clinicians have no time. -Yes, it would provide an understanding of the pain variations. -Yes, it is easier to show what is wrong and where the pain originated. -Yes. Helps to remember where and when it hurts. -Yes. To see the links between the pain and any training or treatment.

5.4 EXPLORING NOVEL PAIN METRICS FOR THE CLINICAL USE OF DIGITAL PAIN MAPPING

Symmetrical pain patterns, as assessed using pain drawings, have been used in low-back pain with distal pain referral, to differentiate between somatic and radicular pain (180). However, the assessment of the spread and consistency of pain distribution over time, may be a more objective outcome to assist in the clinical decision-making process. Therefore, novel pain metrics were used to determine a consistency index and the changes of pain distribution spreading over time using digital pain drawings.

5.4.1 ASSESSMENT OF THE PAIN AND DISCOMFORT CONSISTENCY

Pain distribution is a relevant tool to support the clinical decision-making process (see section 1.1). Pain and discomfort distribution consistency over time or lack thereof, may offer a clearer picture of the pain condition. For example, a diagnosis of neuropathic pain includes an assessment of neuroanatomically plausible pain distribution consistency (181). Furthermore, the identification of a lack of pain

distribution consistency can be used as to identify other causes of pain such as, malignancies (182), appendicitis (183), or aneurysm (184). Therefore, a measure of consistency, such as a pain distribution consistency index could capture the distribution changes over time. A higher consistency index would indicate similar pain and discomfort distribution patterns, as represented in the pain drawings.

The Jaccard index (see section 2.3.1), was used to assess similarities in pain and discomfort distribution among pain drawings and determine a distribution consistency index. The Jaccard index was calculated between two consecutive weekly pain drawings for each of the patients. Results showed that consecutive weekly pain drawings were similar, suggesting pain and discomfort distribution consistency on a weekly basis, at a group level. However, a more clinically relevant distribution consistency index would assess changes in consistency over a longer period, such as from week one to week four, and so on (see section 7.3).

The Jaccard index has been used to assess the level of pain distribution similarity between two pain drawings (75). However, the use of this measure can lead to misinterpretations, as it may miss development of pain in a new area, or a change in the shape of the pain spread from a large centralized area in the buttocks to a thin line from buttocks to foot. Furthermore, the Jaccard index only assesses the similarity between two pain drawings at specific time points, missing spatiotemporal changes in pain distribution over time. The development of novel pain metrics to assess consistency may be a relevant evolution for the clinical application of digital pain mapping. The availability of a pain distribution consistency index during the patients' assessment may provide a novel relevant outcome during the clinical decision-making process.

5.4.2 VISUAL ASSESSMENT OF THE OVERALL PAIN SPREAD

To assess the areas where pain and discomfort was more frequently reported, as well as the bodily spread, heat maps and contour overlays were created. Only pain drawings of the posterior view were explored for the primary pain sites (cervical and low-back pain) and presented for male and female.

Heat maps are used to display frequency visually. The heat maps make for an easy visual comparison of common pain locations (18,76). Therefore, to visualize the frequency of pain, dull aching, stabbing, burning and numbness sensations, heat maps were generated using pain drawings from study II. These heat maps revealed that females with low back pain reported larger patterns of pain that referred from the low-back and lower limb, than the male patients. Additionally, heat maps revealed that females with their primary pain site on the low-back reported burning sensations more frequently on the hands, whereas the male counterparts reported burning sensations more frequently on the feet (Fig. 5-5).

Contour overlays revealed that burning and numbness sensations were perceived as more localized (Fig. 5-6). Additionally, the contours revealed that pain and discomfort were widespread for females, independently of the primary pain site. Similarly, males reported widespread pain and those with back-pain did not report pain in the arms. These results concur with previous findings suggesting that chronic widespread pain is more prevalent in females than males (185,186).

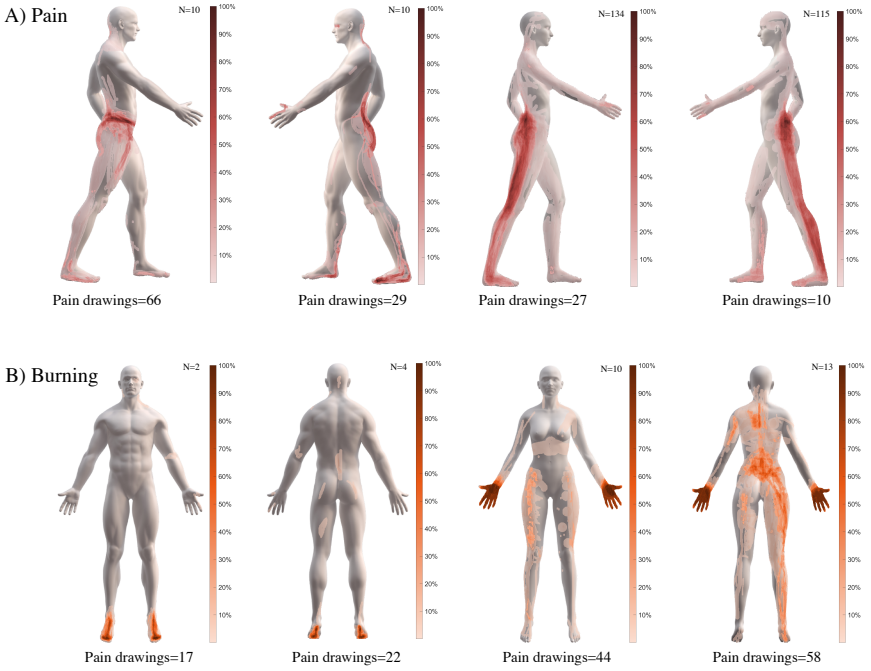

Figure 5-5. Pain heat maps generated by pain drawing overlays of patients with non-malignant chronic spinally referred pain from study II*. Pain heat maps generated from patients with their primary pain site on the low-back, representing (A) pain and (B) burning quality descriptors. The colour gradients indicate the frequency (%) of patients that reported pain and discomfort in the specific location. Darker colours represent the most frequently reported location of pain and discomfort. Each heat map has a different scale displaying the number of participants (N) and the number of pain drawings.*

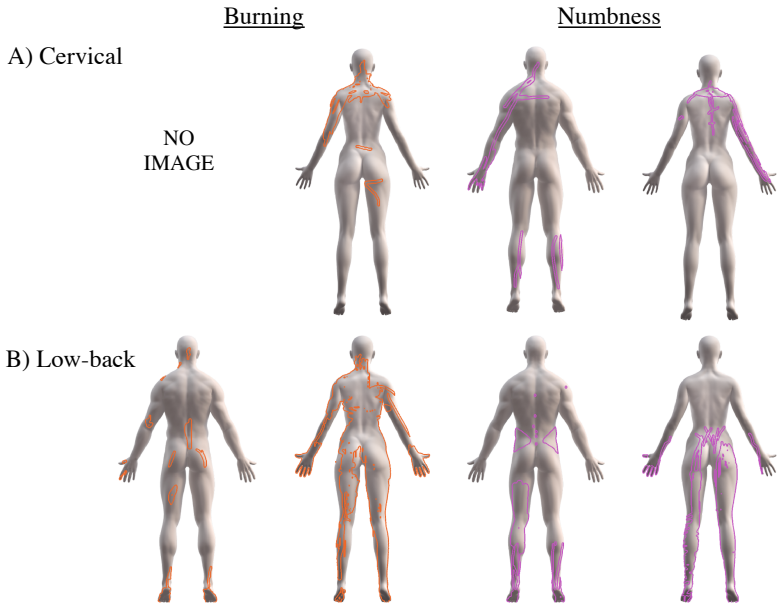

Figure 5-6. Contour overlays generated by pain drawings from patients with non-malignant chronic spinally referred pain from study II*. Contour overlays generated for men, women, and primary pain site (A-cervical and B-low-back) separately. None of the male patients with the primary pain site on the cervical spine reported burning sensations.*

5.4.3 CONCURRENT PAIN AND DISCOMFORT QUALITY DESCRIPTORS

Patients submitting digital pain reports were able to select among a range of 10 pain descriptors, as well as the general descriptor "pain". While selecting among quality descriptors, patients were able to additionally select the intensity of each descriptor among mild, moderate, or severe.

The pain descriptor selection data obtained from the submitted pain reports also allows for novel pain metrics to explore the concurrence or likelihood of reporting a specific quality descriptor, based on the actual selected descriptors. The clinical interest of exploring concurrent pain descriptors can assist towards a condition's quality descriptor pattern prediction and prognosis.

The frequency of mild, moderate, and severe pain with concurrent descriptors was determined to explore quality descriptors reporting patterns. Severe pain was most commonly associated with numbness and throbbing. Similarly, patients that reported tingling were also likely to report stabbing (fig. 5-7).

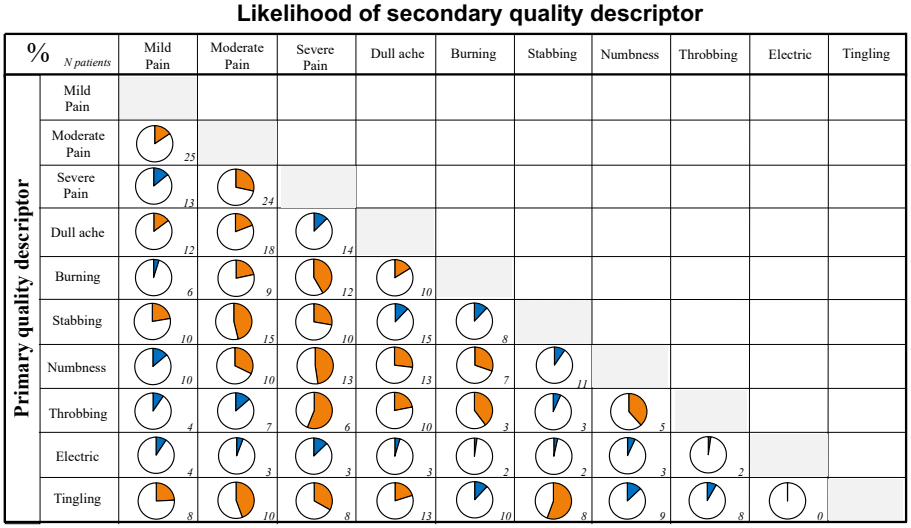

Fig. 5-7. Concurrence of pain and discomfort quality descriptors using digital pain mapping. *The color segments offer an easy visualization of the likelihood ratios of having a second quality (secondary quality descriptor) at the same time as another quality (primary quality). The orange segments represent a likelihood ratio greater than 15%, whereas the blue segments represent a likelihood less than 15%. The italic numbers represent the number of patients with the primary and secondary quality descriptors.*

5.5 LESSONS LEARNT FROM DATA COLLECTION USING DIGITAL PAIN MAPPING IN A CLINICAL POPULATION

Patients recruited online tended to have better retention rates and be more compliant than the patients recruited using the traditional in-house strategy. The online nature of the study allowed for the creation of more engaging recruitment strategies and the development of interactive pathways to deliver information. This pragmatic feasibility study of a web-based pain-mapping app identified insights which may improve online recruitment strategies and reporting compliance in future studies:

- Online-related patient recruitment criteria:
    - Regular access and habitual use of a digital device at home and/or work.
    - Access to at least one more device than a smart phone, such as digital tablet or computer.
    - Technology literacy and confidence in the use of e-mail, the different available devices, and different internet browsers.
    - Name the study with an easy to understand name resulting in a catchy acronym, easy to remember. Use it in all correspondence.

  - Researchers should have continuous access to the recruitment platforms to offer potential recruits a fast turn-around response time.

- Optimization of the online recruitment strategy:
  - Research the social media platform demographic to inform your platform selection.
  - Develop a strategy to maximize social media reach by choosing your preferred audience. Development of recruitment collaborating partners to share and advertise the study online.
  - Creation of a square video format with a maximal duration of 30-60 seconds and a clear descriptive title.
  - State the key message in lay language, contact details and direct access to further information (i.e. website).
  - Official logos and institutional e-mails from the research institution should be used to signal safety and credibility.
  - The message to convey should be clear and reinforced with visual cues.
  - The first three seconds need to be of impact to catch the attention.
  - The video should have captions.
  - Suggest viewers to tap for sound.
  - The researchers should appear in the video to humanize the research.
  - Ease of contact using direct messaging (i.e. *Messenger*) to the platform with a fast response turn-around time.

- Retention and compliance maintenance:
  - Provide the patient with a journey map to level expectations regarding frequency and type of data collection and other forms of contact.
  - Remind the patient to check the junk mailbox regularly.
  - Development of a reminder system to suit the individual needs.
  - Optimization of the user journey and identification of the patients' motivation, technical challenges, and limitations.
  - Development of positive reinforcement strategies, such as rapid feed-back and personalized comments.
  - Rapid response to queries and comments.
  - Personalize feedback using the patients' name and friendly language.
  - Add a photo of the researchers to create familiarity when communicating electronically.
  - Use positive reinforcement strategies.

The online recruitment strategy required approximately 80 hours of work prior involving researchers and videographers. Time for brainstorming, script writing and rehearsing to ultimately record a one-minute video, create a flyer and landing page, as well as upload one post on Facebook. The video recording and production, as well as the printing of the flyers cost a small fee. The flyer had a QR code directing the prospective recruit to a landing page. The landing page had information about the study and the researchers' contact details, and no patients were recruited using this pathway. The recruitment video reached 15,256 people, had over 5,000 unique viewers, and received 281 engagements (clicks, likes, comments and shares) in Denmark. The post was shared 91 times. The top five sharing sites included physiotherapy clinics, pharmacies, and spinal pain patient groups. In addition to the work involved prior recruitment, 10 minutes were required per participant for the screening process (8.5 hours).

In comparison, the traditional in-house strategy required approximately 20 hours prior work to develop documentation, and approximately three two-hour-long meetings with the Head of Department to explain the study and agree on a collaboration. Similarly, the Head of Department used approximately three hours to discuss the study with the department staff and other administrative problem solving. The invitations to participate were added to the electronic appointment, with an estimate of 200 invitations sent, in a six-month period. Each doctor in the department used approximately 10 minutes for every one of the 200 potential recruits (33.5 hours). If the patient agreed to participate, a further three minutes were used to sign the consent form (1.5 hours). These consent forms were then collected from the hospital and delivered to the university. It is estimated that the recruitment strategy required approximately 100 hours in total. Therefore, the traditional in-house recruitment strategy had less direct costs, but required more time, effort, and resources than the online strategy.

To gauge success of each strategy, a cost-benefit ratio was calculated using the basic hourly salary rate of the personnel and expenses incurred per patient recruited. The cost-benefit ratio for the online strategy was approximately 430DKK per participant; whereas the ratio for the traditional strategy was calculated as 1200DKK per participant. The online recruitment strategy resulted in approximately double the number of patients than the traditional in-house recruitment strategy. Additionally, patients recruited online had better reporting compliance. Therefore, the online recruitment strategy may prove to be more time and cost-efficient than the traditional in-house recruitment strategy.

5.6 SUMMARY OF THE MAIN FINDINGS STUDY II (CLINICAL USE)

This PhD project (study II) tracked pain and discomfort remotely using a pain-mapping app, over a prolonged period, in patients with non-malignant chronic spinally referred pain. The main findings were:

- The feasibility of tracking pain remotely in a research project is depending upon retention and compliance. Factors influencing compliance are related to the app (ease-of-use and usability), as well as to the patients' motivation and perceived benefit.

- Patients with a better reporting compliance rate were younger and had been recruited using an online strategy. The online recruitment strategy using social media platforms was more time-efficient than traditional recruitment strategies.

- Barriers of use (technical and communication) need to be overcome to improve compliance. Additionally, positive reinforcement strategies need to be implemented to improve engagement.

- Novel digital metrics were applied as method to quantify pain beyond area (pixels) and intensity measures. These metrics included a distribution consistency index, frequency and contour maps, as well as concurrent quality descriptors likelihood ratio.

CHAPTER 6. NOVEL APPROACHES TO QUANTIFY CHANGES IN THE INTENSITY OF QUALITY DESCRIPTORS

Quality descriptors can help delineate the driving mechanisms of pain (8,9,154), reveal symptom progression (2,9), and help to differentiate between nociceptive, neuropathic pain, and peripheral neuropathies (11,187–189).

In the early 1980s the McGill Pain Questionnaire (MPQ) (13) was developed to assess the quality and the intensity of pain. The MPQ consisted of 78 qualities to describe the sensory and affective dimensions of pain, as well as a body chart. This original version of the MPQ was later modified to and named the Short-form MPQ (14), where the number of pain descriptors was reduced to 15. Additionally, the intensity of each of those 15 descriptors was rated as none, mild, moderate, or severe. Furthermore, the Short-form MPQ (Short-form MPQ-2) was revised and a total of 22 pain descriptors were included alongside a 0-10 NRS (111). Similarly, the Pain Quality Assessment Scale (PQAS) (190) rates the intensity of 16 different pain qualities, as well as the level of unpleasantness, depth, and frequency. The sensory perception of a quality descriptor is influenced by self-awareness, language, and prior experiences (191,192). Changes in sensory perceptions in response to a stimulus are assessed using psychometric tests. However, patients with language barriers and cognitive limitations may be challenged to identify a descriptor to match the perceived sensation.

Digital health solutions have taken a step beyond the current psychometric tests to visualize and quantify sensory perceptions (193,194). The web-based painQUILT app (193,195) uses illustrations or icons to represent the sensory perception. For example, an icon of a hammer to represent a pounding sensation, or a sword to represent stabbing. The Painimation App uses short motion graphics or animations of an illustration with sound effects, instead of using a verbal descriptor to describe the sensory perception (194). For example, Painimation uses an animation of electricity (an angular line moving like a lightning bolt, accompanied by a mains hum sound) to represent the sensation of electrifying. Both apps use an illustration (animated or not) to overcome the language barrier. However, identifying an illustration (i.e. a hammer) with the associated perception (i.e. throbbing descriptor) also requires self-awareness and prior experiences. Additionally, both apps quantify the intensity of the sensory perception using a rating scale, as well as the percentage on the body chart.

Study III (77) aimed to assess the relationship between sensory perceptions and a range of non-painful transcutaneous electrical stimulation. The digital pain-mapping software Animate Pain was used to determine changes in electrically evoked sensory perceptions by adjusting a tingling animation (see section 2.3.2 for a description of study III methods).

6.1 QUANTIFYING SENSORY PERCEPTION USING SELF-ADJUSTED ANIMATIONS (STUDY III)

Participants received a range of randomized transcutaneous electrical stimulations (2, 3, 3.5, 4, 4.5, 5, 5.5 and 6mA) of four seconds duration each. This range was repeated three times to elicit sensory perceptions to healthy participants. Following each stimulation, participants adjusted two digital visual analogue scales (dVAS) to modify the density and speed of the dots from a tingling animation in real-time.

Study III (77) revealed that participants (N=32) systematically adjusted the density parameter of the tingling animation following in a correlated fashion to the intensity of the electrical stimulation (fig. 6-1, A-B). No associations were found for the speed dVAS adjustments.

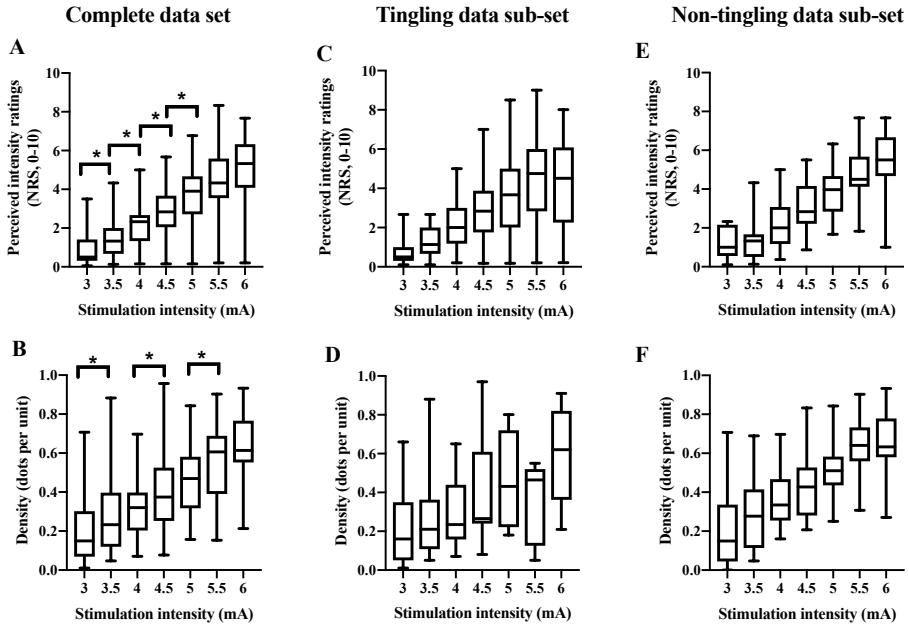

Figure 6-1. Relationships between electrical stimulation intensity, perceived intensity ratings, and density (N=32). *Systematic increases in perceived intensity ratings and density for the tingling animation were associated with increases in electrical stimulation intensity for (A, B) the complete data set (N = 641 perceived stimulations), (C, D) the data sub-set representing perceptions described as tingling (N = 252 stimulations), and (E, F) the data sub-set representing the perceptions not described as tingling (N = 389 stimulations). Significance (*) adjusted for multiple correlations set at P<0.001. Box and whiskers represent the median (line), maximal, and minimal values. Reproduced with permission (Galve Villa et al., 2020)*

Tingling was most frequently selected with the low electrical stimulation range (3 to 4.5mA), with a transition towards the more frequent use of stabbing, drilling, and sharp sensations in the upper electrical stimulation range (4.5 to 6mA) (fig. 6-2). These results suggest that the low electrical stimulation range was appropriate as an experimental tingling model.

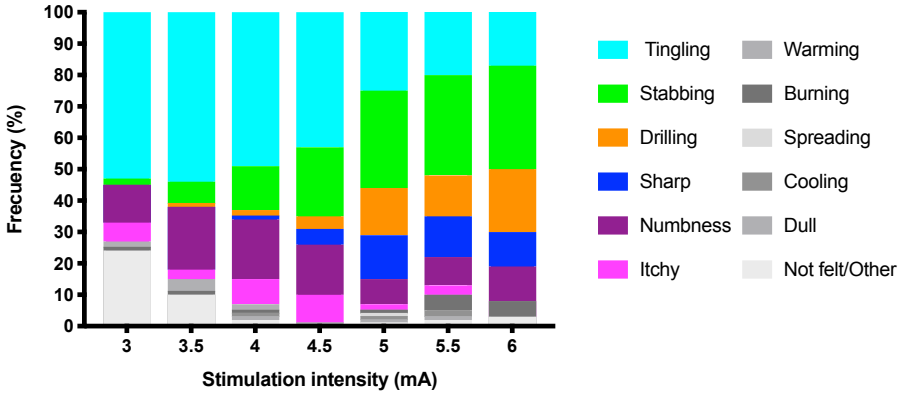

Figure 6-2. Frequency of quality descriptors selection associated with the different electrical stimulations. *The bright colours represent the descriptors most frequently selected during study III. Tingling was most frequently selected from 3 to 4.5mA. Stabbing and drilling had the largest increase in frequency from 4.5 to 6mA, as the frequency of tingling decreased.*

Results from the density adjustments and perceived intensity ratings, as shown in figure 6-1, may be explained by the changes in the descriptor selection. Panels C to F from figure 6-1 show a trend (not significant) in density and intensity ratings as the electrical stimulation increases from the data subsets of the stimulations described as tingling (C-D) and the remaining stimulations (E-F). However, the complete data set (A-B) shows a significant adjustment in density and intensity ratings associated with an increase in stimulation. These results may be explained by the descriptors numbness and itchy. Even though tingling is the most frequently selected descriptor in the low stimulation range, its frequency decreases as the stimulation intensity increases. However, the selection frequency of numbness and itchy has the opposite pattern, increasing from 3-4.0mA. Therefore, the descriptors numbness and itchy from the non-tingling data sub-set are, perhaps, the cause of the different density and intensity ratings results among the complete, tingling, and non-tingling datasets.

The MPQ (13,196) characterizes descriptors into sensory, affective, and evaluative class and 16 subclasses. Within each subclass, the position of each descriptor is based on the relative intensity ranking within that subclass. For example, “hot” appears earlier than “scalding” in the thermal subclass list, as “hot” is ranked as a less intense sensation than “scalding”. This descriptor relative intensity ranking suggests a sensory hierarchy. Our results show a transition from tingling, numbness, and itchy towards drilling, stabbing, and sharp, from the lower to the higher electrical stimulation intensities. These results suggest a hierarchical relationship among these descriptors. In the clinical practice, this hierarchical transition may be useful to suggest disease progression when, for example, a patient reports a tingling sensation has changed to a stabbing sensation. Therefore, the concept of a hierarchy in quality descriptors may be relevant as a tool to identify progression or regression

of pain and discomfort symptoms, supplementary to the concurrent quality descriptors described in section 5.3.3.

The use of the self-adjustable animation revealed that the density parameter was associated with changes in sensory perceptions. These animations may be useful to quantify changes of sensory perceptions, if they can help to overcome language and cognitive barriers. However, this will need further research and validation. Moreover, the assessment of changes in sensory perceptions over time can offer a new temporal dimension into pain mechanisms and assist in the clinical decision-making process.

6.2 PARTICIPANTS' FEEDBACK ON THE ANIMATION

Semi-structured interviews in study III (77) revealed the participants' experience and insights into the adjustment of the tingling animation to visually represent a sensation. The responses obtained from the interviews were transcribed, coded, and grouped into three themes (table 6-1).

Table 6-1. Selected comments describing the appropriateness of the animation, usability issues from the Animate Pain app, and suggestions for improvement (N=34). (Reproduced with permission Galve Villa, 2020).

Appropriateness of the animation	**Usability of Animate Pain**	**Suggestions for improvement**
-Not happy with the speed parameter. -It represents fine the sensations of tingling I felt, but if I see it out of context, I would not think of tingling. -The animation represents well what I felt. -Good baseline animation for this study. -Neither animation nor canvas matched the sensation.	-The speed was confusing and difficult to adjust. -The name "speed" is not appropriate, and I found the scale very confusing to adjust. -Not user-friendly. The grey colours, the scales. -Difficult to put the sensation onto the image. -I liked the hand 3D image. -Easy to adjust. -It is fine. Works well.	-It should have an image of the whole hand. -I would have liked to be able to change the shape of the dots to something sharp, like a triangle. -Change the colour so it is easier to see the dots.

6.2.1 THE APPROPRIATENESS OF THE ANIMATION

Most participants had a good impression about the suitability of the tingling animation ("Good baseline animation for this study", "The animation matched the sensation"). Whereas some participants reported opposite comments ("It didn't fit", "Neither the animation nor the canvas matched the sensation"), suggesting the animation was only suitable to represent a tingling sensation.

6.2.2 THE USABILITY OF THE PAIN MAPPING SOFTWARE

Overall, most of the participants identified difficulties adjusting the speed dVAS ("The speed was confusing and difficult to adjust", "The name speed is not appropriate and is confusing", "Not user-friendly"). Furthermore, some participants reported difficulty adjusting the dVAS as the dots from the animation were difficult to see due to a poor colour contrast (grey dots on grey canvas). A brighter room or a larger screen may have offered an improved visibility. Nonetheless, most of the participants reported that adjusting the density parameter as intuitive.

6.2.3 SUGGESTIONS FOR IMPROVING THE SOFTWARE

Participants most commonly recommended changing the grey colour range of the dots and the canvas, having a canvas with the dorsal aspect of the hand, and modifying the speed dVAS with a more intuitive rating scale. An interesting recommendation was to enable a feature to change in the animation's shape. Such as a feature would change the animation's dots to, for example, triangles to represent the transition from tingling to stabbing.

6.3 SUMMARY OF THE MAIN FINDINGS FROM STUDY III (ANIMATIONS TO QUANTIFY DESCRIPTORS)

Study III used state-of-the-art software allowing momentary adjustments of an animation to quantify changes in perceived intensity, following a range of transcutaneous ES. The animation aimed to visually represent a sensation of tingling with dots appearing and disappearing. The adjustable features from the animation modified the density (number of dots per random unit) and the speed at which the dots appeared and disappeared. The findings from study III revealed that:

- Increases in the animation density were associated with increases in the perceived intensity ratings and intensity of the electrical stimulation. These findings imply that self-adjustable animations may be a useful method to quantify changes of pain and discomfort quality descriptors.

- Increasing the intensity of the ES revealed a hierarchy in quality descriptions where perceptions transitioned from tingling, numbness, and itchy to stabbing, drilling, and sharp. This hierarchy may be useful to clinically assess the progression or regression of pain and discomfort.

- Self-adjustable animations may be a useful tool to assess sensory perceptions beyond pain, overcome language and cognitive barriers, and represent a further advancement to digital pain mapping.

CHAPTER 7. CHALLENGES AND LIMITATIONS OF DIGITAL PAIN MAPPING

Digital pain mapping offers advantages as compared to pen-to-paper pain drawings, such as improving the systematic quantification of pain, and the momentary ecological acquisition of digital pain biomarkers. However, the use of the digital pain-mapping app in patients with non-malignant chronic spinally referred pain was met with challenges and limitations.

7.1 METHODOLOGICAL CHALLENGES

The ability to accurately represent the distribution of a pain perception onto a body chart is a basic limitation when using a pain drawing, as the drawing may be influenced by the individual's body image (197,198) and drawing ability (143). This limitation is equally present when using pen-to-paper and digital pain drawings. Currently, it is unknown whether the individuals' drawing ability will improve by completing pain drawings repeatedly over time, due to motor and cognitive skills improvement with repetition (199,200). Additionally, it is unknown whether improving the digital drawing equipment from a mouse or finger-tip to an S-pen, or modifying the body chart to a more realistic 3D avatar (62,201,202), would influence the drawing ability. Challenges and limitations related to the individual studies are discussed in the following sections.

7.1.1 ASSESSMENT OF MOMENTARY PAIN AND PAIN RECALL ACCURACY (STUDY I)

Participants from study I were asked to report the evoked momentary pain intensity every 30 seconds from onset until pain cessation, following an injection of HS. Additionally, participants were randomized into a drawing or a non-drawing group. Participants from the drawing groups captured the momentary pain intensity and distribution simultaneously. Seven days after the injection of HS, all participants were asked to recall the evoked peak pain intensity and extent (see section 4.1).

The number of participants in each of the four groups may not have been large enough to identify spatiotemporal differences. The high variability of the size of the momentary pain area and the lack of more intense momentary pain may have limited the ability to detect statistical differences (see Fig. 3.1). Specifically, the momentary pain distribution was only captured on 13 participants for each dose. A post-hoc effect size calculation for the size of the peak pain (PP) area showed that 10% of the size was attributable to the group, suggesting the size of the study was underpowered.

The pain area recall accuracy for the non-drawing groups was assessed using the extent of the peak pain area and the pain distribution from the drawing groups, as a reference. The use of the drawing groups' data as a reference may have influenced the recall accuracy assessment between drawing and non-drawing groups. Therefore, undermining the results suggesting a lack of influence in pain recall by the repeated drawing task. A crossover study design, with four sessions and all subjects participating in drawing and non-drawing groups may help overcome this limitation.

7.1.2 LONGITUDINAL STUDIES USING ECOLOGICAL MOMENTARY DATA ACQUISITION (STUDY II)

The advantages of acquiring ecological momentary digital pain biomarkers (see section 1.3) raise methodological challenges due to the lack of standardized quality pain reporting (46,90,203). The quality of the data acquired is a common challenge for longitudinal studies relying on patients to submit information. For example, in study II some patients submitted digital pain reports as requested (weekly), whereas other patients submitted the pain reports too often (pockets of data overload) and others not often enough (pockets of missing data). Results from study II also show differences in the device used (see section 5.1), as well as the quality (drawing style) of the pain drawing (see section 5.2) among patients. Lastly, the comments provided during pain reporting (section 3.4) highlight differences in the reporting context (location and environment). Optimizing data quality may improve the accuracy of the results obtained using remote pain mapping and tracking in future clinical research studies.

The lack of contextual information about factors that may influence the patients' pain experience, such as treatment and activity levels, was not systematically collected during study II. The contextual information provided by the patients' comments (see section 3.4), suggests that detailed information about the individual patient's social environment may open a window to understand improvements in or worsening of pain symptoms. For example, pain may improve after a specific treatment in a patient with a sedentary lifestyle. This pain improvement may lead to a subsequent improvement in mood and an increase in physical activity. This increase in activity can, subsequently, provoke an increase in pain compelling the patient to regress to sedentarism, commencing a "yo-yo effect" or vicious cycle of pain and inactivity (204,205). Awareness of the causes triggering this vicious cycle may contribute to a break in this behavior, leading to better pain self-management.

Longitudinal studies, such as study II, also have limitations regarding the interpretation of results due to confounders (206–208). In study II, time-varying confounders, such as a drawing learning curve, motivation, and external stressors, may have influenced the interpretation of the results. Likely, these time-confounders have influenced the weekly pain fluctuations identified in study II (see section 3.2). For example, feedback from patients (see sections 5.2 and 5.3) revealed that the

zoom and the brush thickness features from the pain mapping app were difficult to use on a small screen (i.e. mobile phone). A device change from a mobile phone to a tablet or laptop during the study, may have improved the usability of the above-mentioned features, therefore, improving the detail of the pain distribution. Similarly, contextual changes, such as holidays, a different bed, a new job, and social events can influence the access to a specific device, the reporting frequency, and the experience of pain, as reflected in the patients' comments (see section 3.4).

These examples show the relevance of how longitudinal data collection should be standardized, when using digital pain mapping in research studies. Standardizing data collection would involve stricter inclusion criteria, with patients committing to submit pain reports at a specific time and frequency, using a pre-set-up device provided by the researchers. Additionally, the development of educational materials, such as a short online interactive course highlighting the common issues identified by study II, instructions about the pain reporting frequency and reminders throughout the study, would align expectations among patients and researchers. Furthermore, developing notification methods to identify pain drawings with possible errors (i.e. drawing a circle around the pain location, rather than drawing the size of the area of pain on the location) would also optimize data quality.

The lack of standardization appears to be common in studies using digital health for data acquisition. A recent review assessed 23 validation studies for 58 wearable devices using a common data collection method (accelerometry) to monitor and report physical activity (209). This review highlighted the variety of methods and reporting outcomes used, some reportedly inappropriate and incomplete, and suggests the need for guidelines to enhance the methodology for digital health studies (209).

7.1.3 ANIMATIONS FOR THE QUANTIFICATION OF CHANGES IN QUALITY DESCRIPTORS (STUDY III)

Study III used a pre-determined animation to visually represent the sensations evoked by a range of electrical stimulation intensities. Therefore, participants were limited to a single animation to depict a range of evoked sensations. Furthermore, participants were limited to represent the spread of the evoked sensations on the volar aspect of the hand, unable to capture any sensations perceived in the dorsal aspect and underestimating the area of spread. Therefore, the results may have reflected a lower size of sensation area. However, results showed a trend of localized spread, rather than referred, evoked sensation. This trend suggests that the lack of area reporting in the dorsal aspect of the hand (referred pain) may not have influenced the results.

There were usability issues with the speed dVAS identified during the feedback with the participants at the end of the session (see section 6.2). The poor usability of the

speed dVAS may have driven participants to adjust the density dVAS, due to a lack of other modifiable features. Modifying the speed dVAS to a more intuitive format, as well as the addition of novel shape-adjusting features, may improve the accuracy of the results in further studies.

7.2 ANALYTICAL LIMITATIONS

Study II used digital pain reports to assess changes in pain and discomfort intensity and extent over time (see section 3.2). Patients were able to report distribution using 11 different quality descriptors. The pain and discomfort extent, as assessed in pixels, was calculated by the sum of all the quality descriptors used in the weekly pain report. However, some pain reports may have had a quality descriptor location overlap, resulting in an overestimation of the pain and discomfort extent.

A pain distribution consistency index was explored as an advanced tool to assist in the clinical decision-making process (see section 5.4.1). However, the Jaccard index results have no clinical implications and the results may be misleading. For example, a high Jaccard index could suggest similarities between two pain drawings with equal pain areas in general but missing other small pain areas with clinical implications (see fig. 5.3). Furthermore, in study II, the Jaccard index assessed the similarity in consecutive pain drawings, determining that pain and discomfort distribution does not change weekly. This suggests that the Jaccard index was not an appropriate measure to assess changes of pain distribution over time.

7.3 SUMMARY OF THE MAIN FINDINGS (CHALLENGES AND LIMITATIONS)

Data collection using digital pain mapping can lead to a range of methodological challenges and limitations. This PhD thesis revealed the following challenges and limitations:

- Study I showed that repeated pain drawings did not influence the accuracy of the pain distribution recall. However, the assessment of the pain recall accuracy in the non-drawing groups may have been influenced by comparing the non-drawing groups' recalled pain drawings with the drawing groups' baseline pain drawings. Therefore, the influence of the repeated pain drawing task may have been underestimated.

- Study II identified methodological challenges due to the lack of standardized acquisition of digital pain biomarkers. Additionally, study II highlighted the need to develop digital pain metrics to explore the consistency of pain drawings over time.

- Study III explored the ability to perceive and visually represent quality descriptors using a self-adjustable animation. However, usability issues related to the speed-adjusting scale may have limited the results.

- The combination of further development of digital health technologies and deeper understanding of the user journey and motivation, as well as an increase in the understanding of the challenges and limitations met by different users (patients and clinicians), will contribute to overcoming these challenges and limitations.

CHAPTER 8. CONCLUSIONS AND FUTURE PERSPECTIVES

The current PhD thesis has addressed three specific objectives: (1) identify and quantify spatiotemporal patterns of experimental and clinical pain intensity, extent, and distribution using digital pain-mapping apps, (2) quantify changes in experimentally evoked tingling sensations using adjustable animations, and (3) determine barriers of use, challenges, and limitations of the different digital pain-mapping technologies utilized.

8.1 CONCLUSIONS

Study I showed dose-response differences of hypertonic saline (HS) evoked-pain intensity, extent, and distribution over time; whereas no differences were identified at peak pain. Pain extent was revealed as a less susceptible outcome to be influenced by pain catastrophizing and perceived stress. Furthermore, study I determined that continuous pain reporting using digital pain drawings does not influence the pain recall accuracy 7-days later. Therefore, these findings support the use of digital pain mapping to capture momentary changes in pain continuously over time. This study implies the importance of pain extent, as well as, pain intensity in the assessment of experimentally evoked pain. These results should be considered in the methodological planning of future studies using HS.

Study II showed fluctuations in intensity and extent in clinical pain, as assessed remotely using digital pain drawings. This study showed that chronic pain may not be as stable as may have been previously thought, and that identifying contextual factors that increase or decrease the pain may be the key to better management. Pain extent was found as being less susceptible to pain catastrophizing, similarly to the findings from study I. However, study II showed that pain extent alongside pain distribution provided clinically relevant data for the pain assessment. Patients' usability assessment suggested that digital pain mapping was a useful and easy-to-use pain communication tool. Therefore, these findings further support digital pain mapping as a clinically relevant tool for the assessment and communication of pain. Study II also identified better compliance rates in younger patients recruited from an online strategy. Online recruitment was revealed as more time and cost-efficient than the traditional in-house recruitment strategy. A checklist was devised for the implementation of online recruitment strategies in future research. This study also highlighted the importance of understanding the patients' motivation to optimize the response compliance rate. These results support the further development of pain mapping technology and exploring its implementation in healthcare settings.

Lastly, study III took a step beyond the classic pain assessment and showed that self-adjustable animations may be a useful tool to quantify changes in sensory

perceptions beyond pain. Additionally, results from study III support the concept of a pain quality hierarchy which may be useful to clinically assess the progression or regression of pain and discomfort.

In summary, the three PhD studies contribute towards the use of remote digital pain mapping and tracking to obtain a more detailed picture of the patients' pain experience. Digital pain mapping can utilize novel digital pain metrics to assess and quantify spatiotemporal patterns of pain and discomfort distribution. These three studies create a platform to visually communicate pain, using self-adjustable animations, to map and track changes in ecological momentary pain and discomfort over prolonged periods. Therefore, digital pain mapping can optimize patient-clinician communication of pain and discomfort.

8.2 FUTURE PERSPECTIVES

The limitations and challenges outlined in this PhD should be used to better inform current and future digital health tools to meet the user's needs. This PhD project underscores the relevance of user-centred design principles to understand the perceived user benefit (patient and clinician) and user journey at the outset. Integrated user-centred methodologies, such as design thinking strategies and co-development approaches during the development process (210,211) may facilitate compliance, adoption, and implementation.

Prospective developments of digital pain mapping may involve the use of 360° 3D body charts, including a non-binary gender chart option, to allow the capture of the pain and discomfort distribution, without spatial limitations, as it spreads around the body. This body chart development could also make use of augmented or virtual reality (201) to capture pain and discomfort distribution, as well as the depth of pain. The use of augmented or virtual reality would allow for self-adjustable animations, rather than the use of colours or intensity rating scales, to quantify changes in pain qualities. While these virtual body charts represent a technology advancement, they would also present technological, accessibility, and methodological challenges.

Machine-learning is a powerful pattern finder and claims to be useful to predict, personalize and, in some cases, prevent pathological processes (212). Future analysis of digital pain drawings may also benefit from machine-learning models. For example, machine learning could improve the quality of the pain drawings by automatically filling out areas of pain from a circle outline, therefore allowing a more accurate account of the pain extent, as assessed in pixels. Additionally, applying machine learning may reveal spatiotemporal patterns of pain and discomfort that may help to manage and predict prognosis in pain conditions (91,213). However, machine-learning models can give false positive presenting results that can be misinterpreted, leading to overdiagnosis or misleading conclusions (214,215). The combination of different pain-mapping technologies to

allow remote ecological momentary assessment (EMA) and the use of animations to capture pain and discomfort over time, together with machine learning, has the potential to disrupt and advance pain assessment in the clinical and research fields. The combination of EMA and monitoring, machine learning analysis, and clinician interpretation may be the next step for pain management and mechanism-based research. A clinical decision-making process, supported by digital biomarkers, may lead to a paradigm shift in diagnosis and treatment of medical conditions.

READING LIST

1. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020 Sep;161(9):1976–82.

2. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. 2005;

3. Giordano J, Abramson K, Boswell MV. Pain assessment: subjectivity, objectivity, and the use of neurotechnology. Pain Physician. 2010 Aug;13(4):305–15.

4. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. J Clin Nurs. 2005 Aug;14(7):798–804.

5. Smith SM, Amtmann D, Askew RL, Gewandter JS, Hunsinger M, Jensen MP, et al. Pain intensity rating training: results from an exploratory study of the ACTTION PROTECCT system. PAIN. 2016 May;157(5):1056–64.

6. IASP. IASP Terminology [Internet]. https://www.iasp-pain.org/. 2017 [cited 2019 Feb 26]. Available from: https://www.iasp-pain.org/terminology?navItemNumber=576

7. IASP Task Force on Taxonomy, edited by H. Merskey and N. Bogduk. Part III: Pain Terms, A Current List with Definitions and Notes on Usage" (pp 209-214) Classification of Chronic Pain [Internet]. Second. Seattle: IASP Press; 1994 [cited 2019 Jul 10]. Available from: https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698&navItemNumber=576#Pain

8. Waterman C, Victor TW, Jensen MP, Gould EM, Gammaitoni AR, Galer BS. The Assessment of Pain Quality: An Item Response Theory Analysis. J Pain. 2010;

9. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations. 2008.

10. Fillingim RB, Loeser JD, Baron R, Edwards RR. Assessment of Chronic Pain: Domains, Methods, and Mechanisms. J Pain. 2016;17(9):T10–T20.

11. Schilder A, Magerl W, Klein T, Treede R-D. Assessment of pain quality reveals distinct differences between nociceptive innervation of low back fascia and muscle in humans. PAIN Rep [Internet]. 2018;3(3). Available from: https://journals.lww.com/painrpts/Fulltext/2018/06000/Assessment_of_pain_quality_reveals_distinct.3.aspx

12. Vilela-Filho O, Cavalcante RBF, Moura MU, Morais BA, Dalle CR, Grandi FT. Pathophysiology of the constant burning, tingling element of neuropathic pain: A new hypothesis. Med Hypotheses. 2014;83(4):441–449.

13. Melzack R. The McGill Pain Questionnaire. 1983. 41–47 p.

14. Melzack R. The short-form McGill Pain Questionnaire. Pain. 1987;30(2):191–7.

15. Hasvik E, Haugen AJ, Gjerstad J, Grøvle L. Assessing neuropathic pain in patients with low back-related leg pain: Comparing the painDETECT Questionnaire with the 2016 NeuPSIG grading system. Eur J Pain U K. 2018;22(6):1160–1169.

16. Freynhagen R, Baron R, Gockel U, Tölle TR. pain \textlessi\textgreaterDETECT\textless/i\textgreater : a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin. 2006;

17. Landmark T, Dale O, Romundstad P, Woodhouse A, Kaasa S, Borchgrevink PC. Development and course of chronic pain over 4 years in the general population: The HUNT pain study. Eur J Pain Lond Engl. 2018;22(9):1606–16.

18. Cruder C, Falla D, Mangili F, Azzimonti L, Araújo LS, Williamon A, et al. Profiling the Location and Extent of Musicians' Pain Using Digital Pain Drawings. Pain Pract. 2018;

19. Shaballout N, Aloumar A, Neubert T-A, Dusch M, Beissner F. Digital Pain Drawings Can Improve Doctors' Understanding of Acute Pain Patients: Survey and Pain Drawing Analysis. JMIR MHealth UHealth. 2019 Jan 10;7(1):e11412.

20. Boudreau SA, Royo AC, Matthews M, Graven-Nielsen T, Kamavuako EN, Slabaugh G, et al. Distinct patterns of variation in the distribution of knee pain. Sci Rep. 2018;8(1):16522.

21. McAnany SJ. Observed Patterns of Cervical Radiculopathy: How Often Do They Differ from a Standard, “Netter-Diagram” Distribution? Spine J. 2017 Oct;17(10):S207–8.

22. Van Boxem K, Van Zundert J, Van Zundert J, Patijn J, van Kleef M. Pseudoradicular and radicular low-back pain: How to diagnose clinically? Vol. 135. 2008. 311–312 p.

23. O’Neill CW, Kurgansky ME, Derby R, Ryan DP. Disc Stimulation and Patterns of Referred Pain: Spine. 2002 Dec;27(24):2776–81.

24. Bertilson BC, Brosjö E, Billing H, Strender L-E. Assessment of nerve involvement in the lumbar spine: agreement between magnetic resonance imaging, physical examination and pain drawing findings. BMC Musculoskelet Disord. 2010 Sep 10;11:202.

25. Bernhoff G, Landén Ludvigsson M, Peterson G, Bertilson BC, Elf M, Peolsson A. The pain drawing as an instrument for identifying cervical spine nerve involvement in chronic whiplash-associated disorders. J Pain Res. 2016 Jun;397.

26. Ohnmeiss DD, Vanharanta H, Ekholm J. Relationship of pain drawings to invasive tests assessing intervertebral disc pathology. Eur Spine J Off Publ Eur Spine Soc Eur Spinal Deform Soc Eur Sect Cerv Spine Res Soc. 1999;8(2):126–31.

27. Baron R, Binder A, Wasner G. Neuropathic pain: Diagnosis, pathophysiological mechanisms, and treatment. Vol. 9. 2010. 807–819 p.

28. Baron R, Binder A, Attal N, Casale R, Dickenson AH, Treede R-D. Neuropathic low back pain in clinical practice. Eur J Pain Lond Engl. 2016;20(6):861–73.

29. Bertilson B, Grunnesjö M, Johansson S-E, Strender L-E. Pain Drawing in the Assessment of Neurogenic Pain and Dysfunction in the Neck/Shoulder Region: Inter-Examiner Reliability and Concordance with Clinical Examination. Pain Med. 2007 Mar;8(2):134–46.

30. Downs MB, Laporte C. Conflicting Dermatome Maps: Educational and Clinical Implications. J Orthop Sports Phys Ther. 2011 Jun;41(6):427–34.

31. Dwyer A, Aprill C, Bogduk N. Cervical zygapophyseal joint pain patterns. I: A study in normal volunteers. Spine. 1990 Jun;15(6):453–7.

32. Aprill C, Dwyer A, Bogduk N. Cervical zygapophyseal joint pain patterns. II: A clinical evaluation. Spine. 1990 Jun;15(6):458–61.

33. Simons DG, Travell JG, Simons LS, Travell JG. Travell & Simons' myofascial pain and dysfunction: the trigger point manual. 2nd ed. Baltimore: Williams & Wilkins; 1999. 1 p.

34. Jung J-H, Kim H-I, Shin D-A, Shin D-G, Lee J-O, Kim H-J, et al. Usefulness of Pain Distribution Pattern Assessment in Decision-Making for the Patients with Lumbar Zygapophyseal and Sacroiliac Joint Arthropathy. J Korean Med Sci. 2007;22(6):1048.

35. Lesher JM, Dreyfuss P, Hager N, Kaplan M, Furman M. Hip Joint Pain Referral Patterns: A Descriptive Study. Pain Med. 2008 Jan;9(1):22–5.

36. Drew MK, Palsson TS, Hirata RP, Izumi M, Lovell G, Welvaert M, et al. Experimental pain in the groin may refer into the lower abdomen: Implications to clinical assessments. J Sci Med Sport. 2017 Oct;20(10):904–9.

37. Vasseljen O, Woodhouse A, Bjørngaard JH akon, Leivseth L. Natural course of acute neck and low back pain in the general population: The HUNT study. Pain. 2013;

38. Grotle M, Brox JI, Veierød MB, Glomsrød B, Lønn JH, Vøllestad NK. Clinical course and prognostic factors in acute low back pain: Patients consulting primary care for the first time. Spine. 2005;

39. Artus M, Van Der Windt D, Jordan KP, Croft PR. The clinical course of low back pain: A meta-analysis comparing outcomes in randomised clinical trials (RCTs) and observational studies. BMC Musculoskelet Disord. 2014;

40. Macedo LG, Maher CG, Latimer J, McAuley JH, Hodges PW, Rogers WT. Nature and Determinants of the Course of Chronic Low Back Pain Over a 12-Month Period: A Cluster Analysis. Phys Ther. 2014 Feb 1;94(2):210–21.

41. Enthoven P, Skargren E, Öberg B. Clinical Course in Patients Seeking Primary Care for Back or Neck Pain: A Prospective 5-Year Follow-Up of Outcome and Health Care Consumption with Subgroup Analysis: Spine. 2004 Nov;29(21):2458–65.

42. Tesarz J, Gerhardt A, Hartmann M, Kohlmann T, Eich W. The Course of the Spatial Extent of Pain in Nonspecific Chronic Back Pain. Clin J Pain. 2016;

43. Grunnesjö M, Bogefeldt J, Blomberg S, Delaney H, Svärdsudd K. The course of pain drawings during a 10-week treatment period in patients with acute and sub-acute low back pain. BMC Musculoskelet Disord. 2006;7:1–9.

44. Palmer H. Pain charts; a description of a technique whereby functional pain may be diagnosed from organic pain. N Z Med J. 1949;

45. Udén A, Landin LA. Pain drawing and myelography in sciatic pain. Clin Orthop. 1987 Mar;(216):124–30.

46. Shaballout N, Neubert T-A, Boudreau S, Beissner F. From Paper to Digital Applications of the Pain Drawing: Systematic Review of Methodological Milestones. JMIR MHealth UHealth. 2019 Sep 5;7(9):e14569.

47. Mooney V, Cairns D, Robertson J. A system for evaluating and treating chronic back disability. West J Med. 1976 May;124(5):370–6.

48. Toomey TC, Gover VF, Jones BN. Spatial distribution of pain: a descriptive characteristic of chronic pain. Pain. 1983 Nov;17(3):289–300.

49. Margolis RB, Tait RC, Krause SJ. A rating system for use with patient pain drawings. Pain. 1986 Jan;24(1):57–65.

50. Escalante A, Lichtenstein MJ, White K, Rios N, Hazuda HP. A method for scoring the pain map of the McGill Pain Questionnaire for use in epidemiologic studies. Aging Milan Italy. 1995 Oct;7(5):358–66.

51. Masferrer R, Prendergast V, Hagell P. Colored pain drawings: preliminary observations in a neurosurgical practice. Eur J Pain Lond Engl. 2003;7(3):213–7.

52. Toomingas A. Characteristics of pain drawings in the neck-shoulder region among the working population. Int Arch Occup Environ Health. 1999 Mar;72(2):98–106.

53. Wallace MS, North J, Grigsby EJ, Kapural L, Sanapati MR, Smith SG, et al. An Integrated Quantitative Index for Measuring Chronic Multisite Pain: The Multiple Areas of Pain (MAP) Study. Pain Med. 2018 Jul 1;19(7):1425–35.

54. Ransford A. O., Cairns D., Mooney V. The Pain Drawing as an Aid to the Psychologic Evaluation oi Patients With Low-Back Pain. Spine. 1(2):127–34.

55. Parker H, Wood PL, Main CJ. The use of the pain drawing as a screening measure to predict psychological distress in chronic low back pain. Spine. 1995 Jan 15;20(2):236–43.

56. Udén A, Aström M, Bergenudd H. Pain drawings in chronic back pain. Spine. 1988 Apr;13(4):389–92.

57. Von Baeyer CL, Bergstrom KJ, Brodwin MG, Brodwin SK. Invalid use of pain drawings in psychological screening of back pain patients. Pain. 1983 May;16(1):103–7.

58. Hildebrandt J, Franz CE, Choroba-Mehnen B, Temme M. The use of pain drawings in screening for psychological involvement in complaints of low-back pain. Spine. 1988 Jun;13(6):681–5.

59. Main CJ, Wood PL, Hollis S, Spanswick CC, Waddell G. The Distress and Risk Assessment Method. A simple patient classification to identify distress and evaluate the risk of poor outcome. Spine. 1992 Jan;17(1):42–52.

60. Tait RC, Chibnall JT, Margolis RB. Pain extent: relations with psychological state, pain severity, pain history, and disability: Pain. 1990 Jun;41(3):295–301.

61. Boudreau SA, Badsberg S, Christensen SW, Egsgaard LL. Digital pain drawings: Assessing touch-screen technology and 3D body schemas. Clin J Pain. 2016;

62. Ghinea G, Spyridonis F, Serif T, Frank AO. 3-D Pain Drawings–-Mobile Data Collection Using a PDA". IEEE Trans Inf Technol Biomed. 2008 Jan;12(1):27–33.

63. Jaatun EAA, Haugen DF, Dahl Y, Kofod-Petersen A. Proceed with Caution: Transition from Paper to Computerized Pain Body Maps. Procedia Comput Sci. 2013;21:398–406.

64. Jamison RN, Washington TA, Gulur P, Fanciullo GJ, Arscott JR, McHugo GJ, et al. Reliability of a preliminary 3-D pain mapping program. Pain Med Malden Mass. 2011 Mar;12(3):344–51.

65. Wenngren A, Stålnacke B-M. Computerized assessment of pain drawing area: A pilot study. Neuropsychiatr Dis Treat. 2009;5:451–6.

66. Mann NH, Brown MD, Enger I. Statistical diagnosis of lumbar spine disorders using computerized patient pain drawings. Comput Biol Med. 1991;21(6):383–97.

67. Sanders NW, Mann NH. Automated scoring of patient pain drawings using artificial neural networks: efforts toward a low back pain triage application. Comput Biol Med. 2000 Sep;30(5):287–98.

68. Mann NH, Brown MD, Enger I. Expert performance in low-back disorder recognition using patient pain drawings. J Spinal Disord. 1992 Sep;5(3):254–9.

69. North RB, Nigrin DJ, Fowler KR, Szymanski RE, Piantadosi S. Automated "pain drawing" analysis by computer-controlled, patient-interactive neurological stimulation system. Pain. 1992 Jul;50(1):51–7.

70. Caseiro M, Woznowski-Vu A, De Oliveira AS, Reis FJJ, Wideman TH. From Paper to Digitalized Body Map: A Reliability Study of the Pain Area. Pain Pract Off J World Inst Pain. 2019 Jul;19(6):602–8.

71. Jaatun E.A.A., Haugen D.F., Dahl Y., Kofod-Petersen A. Designing a reliable pain drawing tool: avoiding interaction flaws by better tailoring to patients' impairments. Pers Ubiquitous Comput. 2015 Jul;19(3–4):635–48.

72. Boudreau SA, Spence R, Vasov G, Egsgaard LL. Feature extraction APP for pain profiles. Biosyst Biorobotics. 2014;7:853–854.

73. Bryner P. Extent measurement in localised low-back pain: a comparison of four methods. Pain. 1994 Nov;59(2):281–5.

74. Egsgaard LL, Christensen TS, Petersen IM, Brønnum DS, Boudreau SA. Do Gender-Specific and High-Resolution Three Dimensional Body Charts Facilitate the Communication of Pain for Women? A Quantitative and Qualitative Study. JMIR Hum Factors. 2016 Jul 20;3(2):e19.

75. Barbero M, Moresi F, Leoni D, Gatti R, Egloff M, Falla D. Test-retest reliability of pain extent and pain location using a novel method for pain drawing analysis. Eur J Pain Lond Engl. 2015 Sep;19(8):1129–38.

76. Boudreau SA, Kamavuako EN, Rathleff MS. Distribution and symmetrical patellofemoral pain patterns as revealed by high-resolution 3D body mapping: A cross-sectional study. BMC Musculoskelet Disord. 2017;18(1).

77. Galve Villa M, D Mørch C, S Palsson T, Boudreau SA. Modifiable motion graphics for capturing sensations. PloS One. 2020;15(2):e0229139.

78. Easton RM, Bendinelli C, Sisak K, Enninghorst N, Regan D, Evans J, et al. Recalled pain scores are not reliable after acute trauma. Injury. 2012;

79. Jensen MP, Mardekian J, Lakshminarayanan M, Boye ME. Validity of 24-h recall ratings of pain severity: Biasing effects of “Peak” and “End” pain. Pain. 2008;

80. Nordin M, Randhawa K, Torres P, Yu H, Haldeman S, Brady O, et al. The Global Spine Care Initiative: a systematic review for the assessment of spine-related complaints in populations with limited resources and in low- and middle-income communities. 2018.

81. Van den Bergh O, Walentynowicz M. Accuracy and bias in retrospective symptom reporting: Curr Opin Psychiatry. 2016 Sep;29(5):302–8.

82. Noel M, Rabbitts JA, Tai GG, Palermo TM. Remembering pain after surgery: A longitudinal examination of the role of pain catastrophizing in children’s and parents’ recall. Pain. 2015;

83. Stone AA, Schwartz JE, Broderick JE, Shiffman SS. Variability of momentary pain predicts recall of weekly pain: A consequence of the peak (or salience) memory heuristic. 2005.

84. Chen E, Zeltzer LK, Craske MG, Katz ER. Children’s memories for painful cancer treatment procedures: Implications for distress. Child Dev. 2000;

85. Gedney JJ, Logan H. Memory for stress-associated acute pain. J Pain. 2004;

86. Lefebvre JC, Keefe FJ. Memory for pain: The relationship of pain catastrophizing to the recall of daily rheumatoid arthritis pain. Clin J Pain. 2002;

87. Pallegama RW, Ariyasinghe S, Perera ED, Treede RD. Influence of Catastrophizing and Personality Traits on Recalled Ratings of Acute Pain Experience in Healthy Young Adults. Pain Med Malden Mass. 2017;

88. Ono M, Schneider S, Junghaenel DU, Stone AA. What Affects the Completion of Ecological Momentary Assessments in Chronic Pain Research? An Individual Patient Data Meta-Analysis. J Med Internet Res. 2019 Feb 5;21(2):e11398.

89. Shiffman S, Stone AA, Hufford MR. Ecological Momentary Assessment. Annu Rev Clin Psychol. 2008 Apr;4(1):1–32.

90. May M, Junghaenel DU, Ono M, Stone AA, Schneider S. Ecological Momentary Assessment Methodology in Chronic Pain Research: A Systematic Review. J Pain. 2018 Jul;19(7):699–716.

91. Meister S, Deiters W, Becker S. Digital health and digital biomarkers – enabling value chains on health data. Curr Dir Biomed Eng [Internet]. 2016 Jan 1 [cited 2020 Feb 26];2(1). Available from: https://www.degruyter.com/view/j/cdbme.2016.2.issue-1/cdbme-2016-0128/cdbme-2016-0128.xml

92. Coravos A, Khozin S, Mandl KD. Developing and adopting safe and effective digital biomarkers to improve patient outcomes. Npj Digit Med. 2019 Dec;2(1):14.

93. Graven-Nielsen T, Arendt-Nielsen L, Svensson P, Jensen TS. Experimental Muscle Pain: A Quantitative Study of Local and Referred Pain in Humans Following Injection of Hypertonic Saline. J Musculoskelet Pain. 1997;

94. Graven-Nielsen T, Arendt-Nielsen L, Svensson P, Jensen TS. Quantification of local and referred muscle pain in humans after sequential i.m. injections of hypertonic saline. Pain. 1997 Jan;69(1–2):111–7.

95. Palsson TS, Boudreau SA, Krebs HJ, Graven-Nielsen T. Experimental Referred Pain Extends Toward Previously Injured Location: An Explorative Study. J Pain. 2018 Oct;19(10):1189–200.

96. Andersen HH, Lo Vecchio S, Gazerani P, Arendt-Nielsen L. Dose-response study of topical allyl isothiocyanate (mustard oil) as a human surrogate model of pain, hyperalgesia, and neurogenic inflammation. Pain. 2017 Sep;158(9):1723–32.

97. Gazerani P, Andersen OK, Arendt-Nielsen L. Site-specific, dose-dependent, and sex-related responses to the experimental pain model induced by intradermal injection of capsaicin to the foreheads and forearms of healthy humans. J Orofac Pain. 2007;21(4):289–302.

98. Sørensen LB, Boudreau SA, Gazerani P, Graven-Nielsen T. Enlarged Areas of Pain and Pressure Hypersensitivityby Spatially Distributed Intramuscular Injections ofLow-Dose Nerve Growth Factor. J Pain Off J Am Pain Soc. 2019 May;20(5):566–76.

99. Staahl C, Drewes AM. Experimental Human Pain Models: A Review of Standardised Methods for Preclinical Testing of Analgesics. Pharmacol Toxicol. 2004 Sep;95(3):97–111.

100. Graven-Nielsen T, Arendt-Nielsen L, Svensson P, Jensen TS. Stimulus-response functions in areas with experimentally induced referred muscle pain--a psychophysical study. Brain Res. 1997 Jan 2;744(1):121–8.

101. Graven-Nielsen T, McArdle A, Phoenix J, Arendt-Nielsen L, Jensen TS, Jackson MJ, et al. In vivo model of muscle pain: quantification of intramuscular chemical, electrical, and pressure changes associated with saline-induced muscle pain in humans. Pain. 1997 Jan;69(1–2):137–43.

102. Mouraux A, Iannetti GD, Plaghki L. Low intensity intra-epidermal electrical stimulation can activate Aδ-nociceptors selectively. Pain. 2010;150(1):199–207.

103. Slopsema JP, Boss JM, Heyboer LA, Tobias CM, Draggoo BP, Finn KE, et al. Natural Sensations Evoked in Distal Extremities Using Surface Electrical Stimulation. Open Biomed Eng J. 2018;

104. Vallbo \AA B. Sensations evoked from the glabrous skin of the human hand by electrical stimulation of unitary mechanosensitive afferents. Brain Res. 1981;215(1–2):359–363.

105. Kellgren JH. A PRELIMINARY ACCOUNT OF REFERRED PAINS ARISING FROM MUSCLE. Br Med J. 1938;1(4035):1029.

106. Janal MN. Concerning the homology of painful experiences and pain descriptors: A multidimensional scaling analysis. Pain. 1996;64(2):373–378.

107. Janal MN, Clark WC, Carroll JD. Multidimensional scaling of painful and innocuous electrocutaneous stimuli: Reliability and individual differences. Percept Psychophys. 1991;50(2):108–116.

108. Steenbergen P, Buitenweg JR, Trojan J, van der Heide EM, van den Heuvel T, Flor H, et al. A system for inducing concurrent tactile and nociceptive sensations at the same site using electrocutaneous stimulation. Behav Res Methods. 2012;44(4):924–933.

109. Clark WC, Carroll JD, Janal MN. A novel method for the construction of verbal rating scales at the ratio scale level of measurement precision: The multidimensional-psychophysical scaling procedure (M-PSP). Atten Percept Psychophys. 2010 Feb;72(2):548–53.

110. Hjermstad MJ, Fayers PM, Haugen DF, Caraceni A, Hanks GW, Loge JH, et al. Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. J Pain Symptom Manage. 2011 Jun;41(6):1073–93.

111. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF. Arthritis Care Res. 2011;63(SUPPL. 11).

112. Boonstra AM, Stewart RE, Köke AJA, Oosterwijk RFA, Swaan JL, Schreurs KMG, et al. Cut-Off Points for Mild, Moderate, and Severe Pain on the Numeric Rating Scale for Pain in Patients with Chronic Musculoskeletal Pain: Variability and Influence of Sex and Catastrophizing. Front Psychol [Internet]. 2016 Sep 30 [cited 2020 Apr 22];7. Available from: http://journal.frontiersin.org/Article/10.3389/fpsyg.2016.01466/abstract

113. Tsze DS, Hirschfeld G, Dayan PS, Bulloch B, von Baeyer CL. Defining No Pain, Mild, Moderate, and Severe Pain Based on the Faces Pain Scale–Revised and Color Analog Scale in Children With Acute Pain: Pediatr Emerg Care. 2018 Aug;34(8):537–44.

114. Delgado DA, Lambert BS, Boutris N, McCulloch PC, Robbins AB, Moreno MR, et al. Validation of Digital Visual Analog Scale Pain Scoring With a Traditional Paper-based Visual Analog Scale in Adults. J Am Acad Orthop Surg Glob Res Rev. 2018 Mar;2(3):e088.

115. Escalona-Marfil C, Coda A, Ruiz-Moreno J, Riu-Gispert LM, Gironès X. Validation of an Electronic Visual Analog Scale mHealth Tool for Acute Pain Assessment: Prospective Cross-Sectional Study. J Med Internet Res. 2020 Feb 12;22(2):e13468.

116. Bird M-L, Callisaya ML, Cannell J, Gibbons T, Smith ST, Ahuja KD. Accuracy, Validity, and Reliability of an Electronic Visual Analog Scale for Pain on a Touch Screen Tablet in Healthy Older Adults: A Clinical Trial. Interact J Med Res. 2016 Jan 14;5(1):e3.

117. Doménech-García V, Skuli Palsson T, Boudreau SA, Herrero P, Graven-Nielsen T. Pressure-induced referred pain areas are more expansive in individuals with a recovered fracture. Pain. 2018 Oct;159(10):1972–9.

118. Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation. Psychol Assess. 1995;7(4):524–32.

119. Michaell JL Sullivan. The Pain Catasthophizing Scale. User Manual [Internet]. [cited 2019 Mar 7]. Available from: https://sullivan-painresearch.mcgill.ca/pdf/pcs/PCSManual_English.pdf

120. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983;24:386–96.

121. Wolf OT, Atsak P, de Quervain DJ, Roozendaal B, Wingenfeld K. Stress and Memory: A Selective Review on Recent Developments in the Understanding of Stress Hormone Effects on Memory and Their Clinical Relevance. Journal of Neuroendocrinology. 2016.

122. Wolf OT. The influence of stress hormones on emotional memory: Relevance for psychopathology. Acta Psychol (Amst). 2008;

123. Shields GS, Doty D, Shields RH, Gower G, Slavich GM, Yonelinas AP. Recent life stress exposure is associated with poorer long-term memory, working memory, and self-reported memory. Stress. 2017;

124. Kim JJ, Song EY, Kosten TA. Stress effects in the hippocampus: Synaptic plasticity and memory. Stress. 2006.

125. Schwabe L, Joëls M, Roozendaal B, Wolf OT, Oitzl MS. Stress effects on memory: An update and integration. Neuroscience and Biobehavioral Reviews. 2012.

126. Schwabe L, Wolf OT, Oitzl MS. Memory formation under stress: Quantity and quality. Neuroscience and Biobehavioral Reviews. 2010.

127. Lluch Girbes E, Duenas L, Barbero M, Falla D, Baert IAC, Meeus M, et al. Expanded Distribution of Pain as a Sign of Central Sensitization in Individuals With Symptomatic Knee Osteoarthritis. Phys Ther. 2016;

128. Bierke S, Petersen W. Influence of anxiety and pain catastrophizing on the course of pain within the first year after uncomplicated total knee replacement: a prospective study. Arch Orthop Trauma Surg. 2017;

129. Dave AJ, Selzer F, Losina E, Klara KM, Collins JE, Usiskin I, et al. Is there an association between whole-body pain with osteoarthritis-related knee pain, pain catastrophizing, and mental health? Clin Orthop. 2015 Dec;473(12):3894–902.

130. Bortsov AV, Platts-Mills TF, Peak DA, Jones JS, Swor RA, Domeier RM, et al. Pain distribution and predictors of widespread pain in the immediate aftermath of motor vehicle collision. Eur J Pain Lond Engl. 2013 Sep;17(8):1243–51.

131. Ris I, Barbero M, Falla D, Larsen MH, Kraft MN, Søgaard K, et al. Pain extent is more strongly associated with disability, psychological factors, and neck muscle function in people with non-traumatic versus traumatic chronic neck pain: a cross sectional study. Eur J Phys Rehabil Med. 2019 Feb;55(1):71–8.

132. Prins MR, van der Wurff P, Groen GJ. Chronic low back pain patients with accompanying leg pain: the relationship between pain extent and pain intensity, disability and health status. J Back Musculoskelet Rehabil. 2013;26(1):55–61.

133. Ohnmeiss DD, Vanharanta H, Estlander AM, Jämsén A. The relationship of disability (Oswestry) and pain drawings to functional testing. Eur Spine J Off Publ Eur Spine Soc Eur Spinal Deform Soc Eur Sect Cerv Spine Res Soc. 2000 Jun;9(3):208–12.

134. Reis F, Guimarães F, Nogueira LC, Meziat-Filho N, Sanchez TA, Wideman T. Association between pain drawing and psychological factors in musculoskeletal chronic pain: A systematic review. Physiother Theory Pract. 2019 Jun;35(6):533–42.

135. Marshall PWM, Schabrun S, Knox MF. Physical activity and the mediating effect of fear, depression, anxiety, and catastrophizing on pain related disability in people with chronic low back pain. PloS One. 2017;12(7):e0180788.

136. Willett MJ, Siebertz M, Petzke F, Erlenwein J, Rushton A, Soldini E, et al. The Extent of Pain Is Associated With Signs of Central Sensitization in Patients With Hip Osteoarthritis. Pain Pract Off J World Inst Pain. 2020;20(3):277–88.

137. Rio E, Girdwood M, Thomas J, Garofalo C, Fortington LV, Docking S. Pain mapping of the anterior knee: injured athletes know best. Scand J Pain. 2018 26;18(3):409–16.

138. Vos CJ, Verhagen AP, Passchier J, Koes BW. Clinical Course and Prognostic Factors in Acute Neck Pain: An Inception Cohort Study in General Practice. Pain Med. 2008 Jul;9(5):572–80.

139. Artus M, van der Windt DA, Jordan KP, Hay EM. Low back pain symptoms show a similar pattern of improvement following a wide range of primary care treatments: A systematic review of randomized clinical trials. Rheumatology. 2010;

140. Gerhardt A, Hartmann M, Blumenstiel K, Tesarz J, Eich W. The prevalence rate and the role of the spatial extent of pain in nonspecific chronic back pain--a population-based study in the south-west of Germany. Pain Med Malden Mass. 2014 Jul;15(7):1200–10.

141. Lei J, You H-J. Variation of pain and vasomotor responses evoked by intramuscular infusion of hypertonic saline in human subjects: influence of gender and its potential neural mechanisms. Brain Res Bull. 2012 Apr 10;87(6):564–70.

142. Lei J, You H-J, Andersen OK, Graven-Nielsen T, Arendt-Nielsen L. Homotopic and heterotopic variation in skin blood flow and temperature following experimental muscle pain in humans. Brain Res. 2008 Sep 26;1232:85–93.

143. Galve Villa M, Cid Royo A, Bjarkam CR, Skuli Palsson T, Boudreau SA. Remote digital pain mapping and tracking in patients with chronic pain. J Med Internet Res. (in press).

144. Barbero M, Fernández-de-Las-Peñas C, Palacios-Ceña M, Cescon C, Falla D. Pain extent is associated with pain intensity but not with widespread pressure or thermal pain sensitivity in women with fibromyalgia syndrome. Clin Rheumatol. 2017 Jun;36(6):1427–32.

145. Miró J, de la Vega R, Tomé-Pires C, Sánchez-Rodríguez E, Castarlenas E, Jensen MP, et al. Pain extent and function in youth with physical disabilities. J Pain Res. 2017;10:113–20.

146. Miró J, Gertz KJ, Carter GT, Jensen MP. Pain location and intensity impacts function in persons with myotonic dystrophy type 1 and facioscapulohumeral dystrophy with chronic pain. Muscle Nerve. 2014 Jun;49(6):900–5.

147. Graven-Nielsen T, Arendt-Nielsen L. Assessment of mechanisms in localized and widespread musculoskeletal pain. Nat Rev Rheumatol. 2010 Oct;6(10):599–606.

148. Martinez-Calderon J, Struyf F, Meeus M, Luque-Suarez A. The association between pain beliefs and pain intensity and/or disability in people with

shoulder pain: A systematic review. Musculoskelet Sci Pract. 2018;37:29–57.

149. Millere A, Kalnberza-Ribule Z, Mezals M, Nulle A, Millere I, Deklava L. Disability, pain catastrophizing and stress coping of patients with low back pain in rehabilitation practice in Latvia. J Back Musculoskelet Rehabil. 2020;33(2):323–8.

150. Wertli MM, Eugster R, Held U, Steurer J, Kofmehl R, Weiser S. Catastrophizing-a prognostic factor for outcome in patients with low back pain: a systematic review. Spine J Off J North Am Spine Soc. 2014 Nov 1;14(11):2639–57.

151. Jensen MP, Johnson LE, Gertz KJ, Galer BS, Gammaitoni AR. The words patients use to describe chronic pain: Implications for measuring pain quality. Pain. 2013;

152. Dworkin RH, Jensen MP, Gammaitoni AR, Olaleye DO, Galer BS. Symptom Profiles Differ in Patients With Neuropathic Versus Non-neuropathic Pain. J Pain. 2007 Feb;8(2):118–26.

153. Fernandez E, Vargas R, Mahometa M, Ramamurthy S, Boyle GJ. Descriptors of pain sensation: A dual hierarchical model of latent structure. J Pain. 2012;13(6):532–536.

154. Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL. Sex, gender, and pain: a review of recent clinical and experimental findings. J Pain Off J Am Pain Soc. 2009 May;10(5):447–85.

155. Rau C-L, Yang J-L, Lin J-J, Wu P-C, Hou C-Y, Song C-Y, et al. Pain quality descriptors and sex-related differences in patients with shoulder pain. J Pain Res. 2018;11:1803–9.

156. Robinson ME, Wise EA, Riley III JL, Atchison JW. Sex differences in clinical pain: a multisample study. J Clin Psychol Med Settings. 1998;5(4):413–24.

157. MacDermid JC, Walton DM, Bobos P, Lomotan M, Carlesso L. A Qualitative Description of Chronic Neck Pain has Implications for Outcome Assessment and Classification. Open Orthop J. 2016;10:746–56.

158. Bennett M. The LANSS Pain Scale: The Leeds assessment of neuropathic symptoms and signs. Pain. 2001;

159. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain. 2005;

160. Tölle TR, Baron R, de Bock E, Junor R, Dias Barbosa C, Marshall SF, et al. painPREDICT: first interim data from the development of a new patient-reported pain questionnaire to predict treatment response using sensory symptom profiles. Curr Med Res Opin. 2019;35(7):1177–85.

161. Foley G, Timonen V. Using Grounded Theory Method to Capture and Analyze Health Care Experiences. Health Serv Res. 2015 Aug;50(4):1195–210.

162. Stynes S, Konstantinou K, Ogollah R, Hay EM, Dunn KM. Clinical diagnostic model for sciatica developed in primary care patients with low back-related leg pain. PloS One. 2018;13(4):e0191852.

163. Stynes S, Konstantinou K, Dunn KM. Classification of patients with low back-related leg pain: a systematic review. BMC Musculoskelet Disord. 2016 23;17:226.

164. Robinson JR. Lower Extremity Pain of Lumbar Spine Origin: Differentiating Somatic Referred and Radicular Pain. J Man Manip Ther. 2003 Oct;11(4):223–34.

165. Khan RS, Ahmed K, Blakeway E, Skapinakis P, Nihoyannopoulos L, MacLeod K, et al. Catastrophizing: A predictive factor for postoperative pain. Am J Surg. 2011;

166. Leeuw M, Goossens MEJB, Linton SJ, Crombez G, Boersma K, Vlaeyen JWS. The Fear-Avoidance Model of Musculoskeletal Pain: Current State of Scientific Evidence. J Behav Med. 2007 Jan 31;30(1):77–94.

167. Koban L, Wager TD. Beyond conformity: Social influences on pain reports and physiology. Emotion. 2016 Feb;16(1):24–32.

168. Edwards RR, Dworkin RH, Sullivan MD, Turk DC, Wasan AD. The Role of Psychosocial Processes in the Development and Maintenance of Chronic Pain. J Pain. 2016 Sep;17(9):T70–92.

169. Eberly L, Richter D, Comerci G, Ocksrider J, Mercer D, Mlady G, et al. Psychosocial and demographic factors influencing pain scores of patients

with knee osteoarthritis. Isales CM, editor. PLOS ONE. 2018 Apr 9;13(4):e0195075.

170. Kristiansen FL, Olesen AE, Brock C, Gazerani P, Petrini L, Mogil JS, et al. The role of pain catastrophizing in experimental pain perception. Pain Pract Off J World Inst Pain. 2014 Mar;14(3):E136-145.

171. Suso-Ribera C, Castilla D, Zaragozá I, Ribera-Canudas MV, Botella C, García-Palacios A. Validity, Reliability, Feasibility, and Usefulness of Pain Monitor, a Multidimensional Smartphone App for Daily Monitoring of Adults with Heterogeneous Chronic Pain: Clin J Pain. 2018 Apr;1.

172. Aaron LA, Mancl L, Turner JA, Sawchuk CN, Klein KM. Reasons for missing interviews in the daily electronic assessment of pain, mood, and stress: Pain. 2004 Jun;109(3):389–98.

173. Stone AA, Shiffman S. Capturing momentary, self-report data: a proposal for reporting guidelines. Ann Behav Med Publ Soc Behav Med. 2002;24(3):236–43.

174. Holthe T, Halvorsrud L, Karterud D, Hoel K-A, Lund A. Usability and acceptability of technology for community-dwelling older adults with mild cognitive impairment and dementia: a systematic literature review. Clin Interv Aging. 2018;13:863–86.

175. Merchant R, Inamdar R, Henderson K, Barrett M, Su JG, Riley J, et al. Digital Health Intervention for Asthma: Patient-Reported Value and Usability. JMIR MHealth UHealth. 2018 Jun 4;6(6):e133.

176. Shaw J, Agarwal P, Desveaux L, Palma DC, Stamenova V, Jamieson T, et al. Beyond "implementation": digital health innovation and service design. Npj Digit Med. 2018 Dec;1(1):48.

177. Steele Gray C. Seeking Meaningful Innovation: Lessons Learned Developing, Evaluating, and Implementing the Electronic Patient-Reported Outcome Tool. J Med Internet Res. 2020 Jul 29;22(7):e17987.

178. Morren M, van Dulmen S, Ouwerkerk J, Bensing J. Compliance with momentary pain measurement using electronic diaries: a systematic review. Eur J Pain Lond Engl. 2009 Apr;13(4):354–65.

179. Salaffi F, Stancati A, Silvestri CA, Ciapetti A, Grassi W. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. Eur J Pain Lond Engl. 2004 Aug;8(4):283–91.

180. Egloff N, Cámara RJA, von Känel R, Klingler N, Marti E, Ferrari M-LG. Pain drawings in somatoform-functional pain. BMC Musculoskelet Disord. 2012 Dec 20;13:257.

181. Finnerup NB, Haroutounian S, Kamerman P, Baron R, Bennett DLH, Bouhassira D, et al. Neuropathic pain: an updated grading system for research and clinical practice. PAIN. 2016 Aug;157(8):1599–606.

182. Verhagen AP, Downie A, Popal N, Maher C, Koes BW. Red flags presented in current low back pain guidelines: a review. Eur Spine J. 2016 Sep;25(9):2788–802.

183. Lee SL, Ho HS. Acute Appendicitis: Is There a Difference between Children and Adults? Am Surg. 2006 May;72(5):409–13.

184. Kwon O-K. Headache and Aneurysm. Neuroimaging Clin N Am. 2019 May;29(2):255–60.

185. Mansfield KE, Sim J, Jordan JL, Jordan KP. A systematic review and meta-analysis of the prevalence of chronic widespread pain in the general population. Pain. 2016 Jan;157(1):55–64.

186. Andrews P, Steultjens M, Riskowski J. Chronic widespread pain prevalence in the general population: A systematic review. Eur J Pain. 2018 Jan;22(1):5–18.

187. Jensen MP, Dworkin RH, Gammaitoni AR, Olaleye DO, Oleka N, Galer BS. Do Pain Qualities and Spatial Characteristics Make Independent Contributions to Interference With Physical and Emotional Functioning? J Pain. 2006;

188. Dworkin RH, Turk DC, Revicki DA, Harding G, Coyne KS, Peirce-Sandner S, et al. Development and initial validation of an expanded and revised version of the Short-form McGill Pain Questionnaire (SF-MPQ-2). Pain. 2009;144(1–2):35–42.

189. Schmid AB, Tampin B. Chapter 10, section 10. Spinally referred back and leg pain. In: Lumbar Spine Online Textbook [Internet]. International Society for the Study of the Lumbar Spine; [cited 2019 Sep 12]. Available from: http://www.wheelessonline.com/ISSLS/section-10-chapter-10-spinally-referred-back-and-leg-pain/

190. Victor TW, Jensen MP, Gammaitoni AR, Gould EM, White RE, Galer BS. The Dimensions of Pain Quality: Factor Analysis of the Pain Quality Assessment Scale. Clin J Pain. 2008;

191. Fernandez E, Krusz JC, Hall S. Parsimonious collection of pain descriptors: Classification and calibration by pain patients. J Pain. 2011;12(4):444–450.

192. Wilson Dianne; Williams Marie; Butler David. Language and the pain experience. Physiother Res Int. 2008;4(1):56–65.

193. Lalloo C, Kumbhare D, Stinson JN, Henry JL. Pain-QuILT: Clinical feasibility of a web-based visual pain assessment tool in adults with chronic pain. J Med Internet Res. 2014;

194. Jonassaint C, Rao N, Sciuto A, Switzer G, De Castro L, Kato G, et al. Using Abstract Animations as an Innovative Technology-Based Approach to Measuring Pain in Adults (Preprint). J Med Internet Res [Internet]. 2018 Feb; Available from: http://preprints.jmir.org/preprint/10056/accepted

195. Lalloo C, Stinson JN, Hochman JR, Adachi JD, Henry JL. Adapting the Iconic Pain Assessment Tool Version 2 (IPAT2) for Adults and Adolescents With Arthritis Pain Through Usability Testing and Refinement of Pain Quality Icons: Clin J Pain. 2013 Mar;29(3):253–64.

196. Melzack R. The McGill Pain Questionnaire: Major properties and scoring methods. Pain. 1975;1(3):277–299.

197. Nishigami T, Mibu A, Osumi M, Son K, Yamamoto S, Kajiwara S, et al. Are tactile acuity and clinical symptoms related to differences in perceived body image in patients with chronic nonspecific lower back pain? Man Ther. 2015 Feb;20(1):63–7.

198. Adamczyk WM, Luedtke K, Saulicz O, Saulicz E. Sensory dissociation in chronic low back pain: Two case reports. Physiother Theory Pract. 2018 Aug;34(8):643–51.

199. Lee TD, Swanson LR, Hall AL. What Is Repeated in a Repetition? Effects of Practice Conditions on Motor Skill Acquisition. Phys Ther. 1991 Feb 1;71(2):150–6.

200. Magallón S, Narbona J, Crespo-Eguílaz N. Acquisition of Motor and Cognitive Skills through Repetition in Typically Developing Children. Ito E, editor. PLOS ONE. 2016 Jul 6;11(7):e0158684.

201. Spyridonis F, Hansen J, Grønli T-M, Ghinea G. PainDroid: an android-based virtual reality application for pain assessment. Multimed Tools Appl. 2014 Sep;72(1):191–206.

202. Turton AJ, Palmer M, Grieve S, Moss TP, Lewis J, McCabe CS. Evaluation of a Prototype Tool for Communicating Body Perception Disturbances in Complex Regional Pain Syndrome. Front Hum Neurosci [Internet]. 2013 [cited 2019 May 7];7. Available from: http://journal.frontiersin.org/article/10.3389/fnhum.2013.00517/abstract

203. Stone AA, Broderick JE, Schwartz JE, Shiffman S, Litcher-Kelly L, Calvanese P. Intensive momentary reporting of pain with an electronic diary: reactivity, compliance, and patient satisfaction. Pain. 2003 Jul;104(1–2):343–51.

204. Vaegter HB, Fehrmann E, Gajsar H, Kreddig N. Endogenous Modulation of Pain: The Role of Exercise, Stress, and Cognitions in Humans. Clin J Pain. 2020 Mar;36(3):150–61.

205. Daenen L, Varkey E, Kellmann M, Nijs J. Exercise, not to exercise, or how to exercise in patients with chronic pain? Applying science to practice. Clin J Pain. 2015 Feb;31(2):108–14.

206. Farrington DP. Longitudinal research strategies: advantages, problems, and prospects. J Am Acad Child Adolesc Psychiatry. 1991 May;30(3):369–74.

207. Palta M, Yao TJ. Analysis of longitudinal data with unmeasured confounders. Biometrics. 1991 Dec;47(4):1355–69.

208. Pierce M, Dunn G, Millar T. Confounding in longitudinal studies in addiction treatment research. Addict Res Theory. 2017 May 4;25(3):236–42.

209. Welk GJ, Bai Y, Lee J-M, Godino J, Saint-Maurice PF, Carr L. Standardizing Analytic Methods and Reporting in Activity Monitor Validation Studies: Med Sci Sports Exerc. 2019 Mar;1.

210. Chokshi SK, Mann DM. Innovating From Within: A Process Model for User-Centered Digital Development in Academic Medical Centers. JMIR Hum Factors. 2018 Dec 19;5(4):e11048.

211. Arevian AC, O'Hora J, Jones F, Mango J, Jones L, Williams PG, et al. Participatory Technology Development to Enhance Community Resilience. Ethn Dis. 2018;28(Suppl 2):493–502.

212. Alonso-Betanzos A, Bolón-Canedo V. Big-Data Analysis, Cluster Analysis, and Machine-Learning Approaches. Adv Exp Med Biol. 2018;1065:607–26.

213. Nam KH, Kim DH, Choi BK, Han IH. Internet of Things, Digital Biomarker, and Artificial Intelligence in Spine: Current and Future Perspectives. Neurospine. 2019 Dec 31;16(4):705–11.

214. Riley P. Three pitfalls to avoid in machine learning. Nature. 2019 Aug;572(7767):27–9.

215. Vogt H, Green S, Ekstrøm CT, Brodersen J. How precision medicine and screening with big data could increase overdiagnosis. BMJ. 2019 Sep 13;l5270.

216. Margoles M. Letter to the editor. PAIN. 1980;8:115–7.

217. Margolis RB, Krause SJ, Tait RC. Lateralization of chronic pain. PAIN. 1985;23:289–93.

218. Fordyce WE, Brockway JA, Bergman JA, Spengler D. Acute Back Pain: A Control-Group Comparison of Behavioral vs Traditional Management Methods. J Behav Med. 1986;9(2).

219. Gatchel RJ, Mayer TG, Capra P, Diamond P, Barnett J. Quantification of lumbar function. Part 6: The use of psychological measures in guiding physical functional restoration. Spine. 1986 Feb;11(1):36–42.

220. Cummings GS, Routan JL. Accuracy of the unassisted pain drawings by patients with chronic pain. J Orthop Sports Phys Ther. 1987;8(8):391–6.

221. Donelson R, Grant W, Kamps C, Medcalf R. Pain response to sagittal end-range spinal motion. A prospective, randomized, multicentered trial. Spine. 1991 Jun;16(6 Suppl):S206-212.

222. Toomey TC, Mann JD, Abashian S, Thompson-Pope S. Relationship of pain drawing scores to ratings of pain description and function. Clin J Pain. 1991 Dec;7(4):269–74.

223. Mann NH, Brown MD. Artificial intelligence in the diagnosis of low back pain. Orthop Clin North Am. 1991 Apr;22(2):303–14.

224. Sivik TM, Gustafsson E, Olsson KK. Differential diagnosis of low-back pain patients: A simple quantification of the pain drawing. Nord J Psychiatry. 1992 Jan;46(1):55–62.

225. Bolton JE, Christensen MN. Back pain distribution patterns: relationship to subjective measures of pain severity and disability. J Manipulative Physiol Ther. 1994 May;17(4):211–8.

226. Escalante A, Lichtenstein MJ, Lawrence VA, Roberson M, Hazuda HP. Where does it hurt? Stability of recordings of pain location using the McGill Pain Map. J Rheumatol. 1996 Oct;23(10):1788–93.

227. Ohlund C, Eek C, Palmbald S, Areskoug B, Nachemson A. Quantified pain drawing in subacute low back pain. Validation in a nonselected outpatient industrial sample. Spine. 1996 May 1;21(9):1021–30; discussion 1031.

228. Brismar H, Vucetic N, Svensson O. Pain patterns in lumbar disc hernia Drawings compared to surgical findings in 159 patients. Acta Orthop Scand. 1996 Oct;67(5):470–2.

229. Türp JC, Kowalski CJ, Stohler CS. Greater disability with increased pain involvement, pain intensity and depressive preoccupation. Eur J Pain Lond Engl. 1997;1(4):271–7.

230. Ohnmeiss DD, Vanharanta H, Ekholm J. Degree of disc disruption and lower extremity pain. Spine. 1997 Jul 15;22(14):1600–5.

231. Sturesson B, Udén G, Udén A. Pain pattern in pregnancy and “catching” of the leg in pregnant women with posterior pelvic pain. Spine. 1997 Aug 15;22(16):1880–3; discussion 1884.

232. Roach KE, Brown MD, Dunigan KM, Kusek CL, Walas M. Test-retest reliability of patient reports of low back pain. J Orthop Sports Phys Ther. 1997 Nov;26(5):253–9.

233. Türp JC, Kowalski CJ, O’Leary N, Stohler CS. Pain maps from facial pain patients indicate a broad pain geography. J Dent Res. 1998 Jun;77(6):1465–72.

234. Alo KM, Yland MJ, Kramer DL, Charnov JH, Redko V. Computer assisted and patient interactive programming of dual octrode spinal cord stimulation in the treatment of chronic pain. Neuromodulation J Int Neuromodulation Soc. 1998 Jan;1(1):30–45.

235. Reigo T, Tropp H, Timpka T. Pain drawing evaluation--the problem with the clinically biased surgeon. Intra- and interobserver agreement in 50 cases related to clinical bias. Acta Orthop Scand. 1998 Aug;69(4):408–11.

236. Ohnmeiss DD, Vanharanta H, Ekholm J. Relation between pain location and disc pathology: a study of pain drawings and CT/discography. Clin J Pain. 1999 Sep;15(3):210–7.

237. Türp JC, Kowalski CJ, Stohler CS. Generic pain intensity scores are affected by painful comorbidity. J Orofac Pain. 2000;14(1):47–51.

238. Ghinea G, Gill D, Frank A, de Souza LH. Using geographical information systems for management of back-pain data. J Manag Med. 2002;16(2–3):219–37.

239. Gagliese L, Melzack R. Age-related differences in the qualities but not the intensity of chronic pain. Pain. 2003 Aug;104(3):597–608.

240. Bertilson BC, Grunnesjö M, Strender L-E. Reliability of clinical tests in the assessment of patients with neck/shoulder problems-impact of history. Spine. 2003 Oct 1;28(19):2222–31.

241. North RB, Calkins S-K, Campbell DS, Sieracki JM, Piantadosi S, Daly MJ, et al. Automated, patient-interactive, spinal cord stimulator adjustment: a randomized controlled trial. Neurosurgery. 2003 Mar;52(3):572–80; discussion 579-580.

242. Jamison RN, Fanciullo GJ, Baird JC. Computerized dynamic assessment of pain: comparison of chronic pain patients and healthy controls. Pain Med Malden Mass. 2004 Jun;5(2):168–77.

243. Hwang M, Kang YK, Shin JY, Kim DH. Referred pain pattern of the abductor pollicis longus muscle. Am J Phys Med Rehabil. 2005 Aug;84(8):593–7.

244. Gibson J, Frank A. Pain experienced by electric-powered chair users: a pilot exploration using pain drawings. Physiother Res Int. 2005 Jun;10(2):110–5.

245. Slipman CW, Plastaras C, Patel R, Isaac Z, Chow D, Garvan C, et al. Provocative cervical discography symptom mapping. Spine J. 2005 Jul;5(4):381–8.

246. Cornwall J, John Harris A, Mercer SR. The lumbar multifidus muscle and patterns of pain. Man Ther. 2006 Feb;11(1):40–5.

247. Friedrich M, Gittler G, Pieler-Bruha E. Misleading history of pain location in 51 patients with osteoporotic vertebral fractures. Eur Spine J Off Publ Eur

Spine Soc Eur Spinal Deform Soc Eur Sect Cerv Spine Res Soc. 2006 Dec;15(12):1797–800.

248. Carnes D, Parsons S, Ashby D, Breen A, Foster NE, Pincus T, et al. Chronic musculoskeletal pain rarely presents in a single body site: results from a UK population study. Rheumatol Oxf Engl. 2007 Jul;46(7):1168–70.

249. Linder J, Svensson O. The impact of pain and depression on assessment of rehabilitation need: a cross-sectional study in long-term sick-listed patients. Int J Rehabil Res Int Z Rehabil Rev Int Rech Readaptation. 2007 Sep;30(3):255–60.

250. Thompson LR, Boudreau R, Hannon MJ, Newman AB, Chu CR, Jansen M, et al. The knee pain map: reliability of a method to identify knee pain location and pattern. Arthritis Rheum. 2009 Jun 15;61(6):725–31.

251. McClish DK, Smith WR, Dahman BA, Levenson JL, Roberts JD, Penberthy LT, et al. Pain site frequency and location in sickle cell disease: the PiSCES project. Pain. 2009 Sep;145(1–2):246–51.

252. Felix E, Galoian K, Aarons C, Brown M, Kearing S, Heiss U. Utility of Quantitative Computerized PainDrawings in a Sample of Spinal StenosisPatients. Pain Med. 2010;11:382–9.

253. Jud SM, Fasching PA, Maihöfner C, Heusinger K, Loehberg CR, Hatko R, et al. Pain perception and detailed visual pain mapping in breast cancer survivors. Breast Cancer Res Treat. 2010 Jan;119(1):105–10.

254. Persson AL, Garametsos S, Pedersen J. Computer-aided surface estimation of pain drawings - intra- and inter-rater reliability. J Pain Res. 2011;4:135–41.

255. Elson DW, Jones S, Caplan N, Stewart S, St Clair Gibson A, Kader DF. The photographic knee pain map: Locating knee pain with an instrument developed for diagnostic, communication and research purposes. The Knee. 2011 Dec;18(6):417–23.

256. Alonso-Blanco C, Fernández-de-Las-Peñas C, de-la-Llave-Rincón AI, Zarco-Moreno P, Galán-Del-Río F, Svensson P. Characteristics of referred muscle pain to the head from active trigger points in women with myofascial temporomandibular pain and fibromyalgia syndrome. J Headache Pain. 2012 Nov;13(8):625–37.

257. Pierce H, Homer CSE, Dahlen HG, King J. Pregnancy-Related Lumbopelvic Pain: Listening to Australian Women. Nurs Res Pract. 2012;2012:1–10.

258. Renner SP, Boosz AS, Burghaus S, Maihöfner C, Beckmann MW, Fasching PA, et al. Visual pain mapping in endometriosis. Arch Gynecol Obstet. 2012 Sep;286(3):687–93.

259. Chatterton BD, Muller S, Thomas MJ, Menz HB, Rome K, Roddy E. Inter and intra-rater repeatability of the scoring of foot pain drawings. J Foot Ankle Res. 2013 Nov 1;6(1):44.

260. Southerst D, Stupar M, Côté P, Mior S, Stern P. The Reliability of Measuring Pain Distribution and Location Using Body Pain Diagrams in Patients With Acute Whiplash-Associated Disorders. J Manipulative Physiol Ther. 2013 Sep;36(7):395–402.

261. Gumina S, Candela V, Passaretti D, Venditto T, Carbone S, Arceri V, et al. Intensity and distribution of shoulder pain in patients with different sized postero-superior rotator cuff tears. J Shoulder Elbow Surg. 2014 Jun;23(6):807–13.

262. Tucker KJ, Fels M, Walker SR, Hodges PW. Comparison of location, depth, quality, and intensity of experimentally induced pain in 6 low back muscles. Clin J Pain. 2014 Sep;30(9):800–8.

263. Barmettler G, Brawn J, Maleki N, Scrivani S, Burstein R, Becerra L, et al. A new electronic diary tool for mapping and tracking spatial and temporal head pain patterns in migraine. Cephalalgia Int J Headache. 2015 Apr;35(5):417–25.

264. Nickel JC, Tripp DA, International Interstitial Cystitis Study Group. Clinical and psychological parameters associated with pain pattern phenotypes in women with interstitial cystitis/bladder pain syndrome. J Urol. 2015 Jan;193(1):138–44.

265. Torstensson T, Butler S, Lindgren A, Peterson M, Eriksson M, Kristiansson P. Referred Pain Patterns Provoked on Intra-Pelvic Structures among Women with and without Chronic Pelvic Pain: A Descriptive Study. Price TJ, editor. PLOS ONE. 2015 Mar 20;10(3):e0119542.

266. van Hecke O, Kamerman PR, Attal N, Baron R, Bjornsdottir G, Bennett DLH, et al. Neuropathic pain phenotyping by international consensus (NeuroPPIC) for genetic studies: a NeuPSIG systematic review, Delphi

survey, and expert panel recommendations. Pain. 2015 Nov;156(11):2337–53.

267. Van Ginckel A, Bennell KL, Campbell PK, Wrigley TV, Hunter DJ, Hinman RS. Location of knee pain in medial knee osteoarthritis: patterns and associations with self-reported clinical symptoms. Osteoarthritis Cartilage. 2016;24(7):1135–42.

268. Hawkins JM, Schmidt JE, Hargitai IA, Johnson JF, Howard RS, Bertrand PM. Multimodal Assessment of Body Pain in Orofacial Pain Patients. Pain Med Malden Mass. 2016 Feb 10;

269. Falla D, Peolsson A, Peterson G, Ludvigsson ML, Soldini E, Schneebeli A, et al. Perceived pain extent is associated with disability, depression and self-efficacy in individuals with whiplash-associated disorders. Eur J Pain Lond Engl. 2016;20(9):1490–501.

270. Poulsen E, Overgaard S, Vestergaard JT, Christensen HW, Hartvigsen J. Pain distribution in primary care patients with hip osteoarthritis. Fam Pract. 2016 Dec;33(6):601–6.

271. Zhang, C., Kjellström, H, Ek, C. H., Bertilson, B.C. Diagnostic Prediction Using Discomfort Drawings with IBTM. Proc Mach Learn Healthc. 2016;56.

272. Candela V, Giannicola G, Passaretti D, Venditto T, Gumina S. Adhesive capsulitis of the shoulder: pain intensity and distribution. Musculoskelet Surg. 2017 Dec;101(Suppl 2):153–8.

273. Rio E, Girdwood M, Thomas J, Garofalo C, Fortington LV, Docking S. Pain mapping of the anterior knee: injured athletes know best. Scand J Pain. 2018 26;18(3):409–16.

274. Neubert T-A, Dusch M, Karst M, Beissner F. Designing a Tablet-Based Software App for Mapping Bodily Symptoms: Usability Evaluation and Reproducibility Analysis. JMIR MHealth UHealth. 2018 May 30;6(5):e127.

275. Wallace MS, North J, Grigsby EJ, Kapural L, Sanapati MR, Smith SG, et al. An Integrated Quantitative Index for Measuring Chronic Multisite Pain: The Multiple Areas of Pain (MAP) Study. Pain Med Malden Mass. 2018 Feb 21;

276. Swinnen TW, Westhovens R, Dankaerts W, de Vlam K. Widespread pain in axial spondyloarthritis: clinical importance and gender differences. Arthritis Res Ther. 2018 27;20(1):156.

277. Fernández-de-Las-Peñas C, Falla D, Palacios-Ceña M, De-la-Llave-Rincón AI, Schneebeli A, Barbero M. Perceived Pain Extent Is Not Associated with Physical, Psychological, or Psychophysical Outcomes in Women with Carpal Tunnel Syndrome. Pain Med Malden Mass. 2019 01;20(6):1185–92.

APPENDIX. SUMMARY OF STUDIES USING PAIN DRAWINGS

This table shows the evolution of pain drawings and the changes in the use and patient population about time. Pain drawings' methodological milestones, as inspired by Shaballout (46), in the areas of concept development (*), data acquisition (#), data analysis (§), and visualization (¤) are highlighted in the table (N/A=not applicable).

Authors	Year	Study population	Main findings
Palmer (44) # §	1949	Patients with pain	Symmetry in the pain drawings can differentiate between organic and functional nervous disorders.
Melzack (196) *	1975	N/A	Development of the McGill Pain Questionnaire scoring system.
Mooney, Cairns, Robertson (47) *	1976	Patients with prolonged pain disability	Evaluation of five methods to assess psychological treatment.
Ransford, Cairns, Mooney (54) §	1976	Patients with low-back pain	A pain drawing scoring system is associated with hypochondriasis and hysteria.
Margoles (216) *#	1980	N/A	Proposition for a standardized body charts template with four views to cover all body areas.
Toomey, Gover, Jones (48) # §	1983	Patients with chronic facial, back, or extremity pain	Spatial distribution of pain sites can be a useful clinical indicator of psychological disturbance.
Margolis, Krause, Tait (217) §	1985	Patients with chronic pain	Development of a pain drawing lateralization scoring system based on the number of body areas.
Fordyce et al. (218) §	1986	Patients with acute low-back pain	Patients from the behavioral treatment group had returned to pre-pain onset outcomes at the 9-12 months follow up.

Gatchel et al. (219) §	1986	Patients with chronic low-back pain	Multi-modal pain management improves psychological outcomes and physical function.
Margolis, Tait, Kraus (49) §	1986	Patients with chronic low-back pain	A body surface scoring system can predict psychological distress or disfunction.
Cummings, Routan (220) * §	1987	Patients with chronic pain	The area of pain is more accurately represented by doctors-driven pain drawings, than patient self-reported pain drawings.
Udén, Landin (45) * # §	1987	Patients with clinical suspicion of a prolapsed disc	Pain drawings alone cannot predict the presence or absence of a prolapsed disc.
Hldebrandt et al. (58) * §	1988	Patients with low-back pain	A pain drawing scoring system is unable to screen for psychological impairment.
Donelson et al. (221) §	1991	Patients with nonspecific low-back pain with or without referred leg pain	The location of referred pain and the intensity of central and referred pain can be changed by spinal flexion and extension movements.
Toomey et al. (222)	1991	Patients with chronic pain	Pain distribution may be a clinically relevant marker of disability in patients with chronic pain.
Mann, Brown (223) # § ¤	1991	Patients with low-back pain	Development of an artificial neuronal network to recognize patterns of pain description using pain drawings.
Mann, Brown, Enger (66) # §	1991	Patients with low-back pain	A computerized statistical method can assist to classify pain drawings into different lumbar spine disorders.
Sivik, Gustafsson, Klingberg Olsson (224) §	1992	Patients with back pain	The frequency scoring of pain drawing can be used as a screening tool for psychological vulnerability.
North el at. (69) # §	1992	Patients with spinal cord stimulator	Computerized analysis can be useful to indicate the electrodes' positioning.

Bryner (73) # §	1994	Patients with low-back pain	Grid-based assessments of pain drawings can overestimate small areas of pain.
Bolton, Christensen (225)	1994	Patients with low-back pain	Pain distribution, but not extent, can assist towards subgrouping of patient with back pain.
Escalante et al. (50) §	1995	Community-dwelling elderly participants	Development of a scoring system for the McGill Pain body chart.
Parker, Wood, Main (55) §	1995	Patients with chronic low-back pain	Three pain drawing scoring systems cannot differentiate patients with psychological distress, between organic and non-organic pain patterns.
Escalante et al. (226)	1996	Rheumatology and post-surgical patients	Validation of a scoring system for the McGill Pain body chart to assess pain distribution.
Ohlund et al. (227)	1996	Blue collar workers	A body area score of pain extent may be a useful screening for the low-back pain prevention.
Brismar, Vucetic, Svensson (228)	1996	Patients referred to lumbar disc surgery	A pain drawing scoring system is not supported as a pre-operative psychological screening tool
Türp, Kowalski, Stohler (229) §	1997	Female patients with chronic facial pain	Pain intensity, pain distribution and high scores in the Beck depression inventory are significant predictors for pain-related disability.
Ohnmeiss, Vanharanta, Ekholm (230)	1997	Patients undergoing discography	Spinal discs may refer pain to the lower limb.
Sturesson, Udén, Udén (231)	1997	Pregnant women	Women with posterior pelvic tilt are more likely to have referred leg pain.
Roach et al. (232)	1997	Patients with low-back pain	Pain intensity, pain drawings and a position questionnaire have a good test-retest reliability.

Türp et al. (233)	1998	Female patients with chronic facial pain	Widespread pain is prevalent in patients with chronic facial pain.
Alo et al (234) #	1998	Patients with spinal cord stimulator	Multiple electrodes and stimulation programs can reduce pain intensity and increase paresthesia overlap.
Reigo, Troop, Timpka (235) #	1998	Patients with low-back pain	Knowledge of the patient's clinical history influences the scoring of pain drawings.
Ohnmeiss, Vanharanta, Ekholm (236)	1999	Patients with low-back pain with or without leg pain	Pain drawings may be a co-adjuvant diagnostic tool to identify the disc level associated with the pain.
Toomingas (52) *	1999	Middle-age workers	Symmetrical neck and shoulder pain distribution are characterized based on duration and severity.
Sanders, Mann (67) # §	2000		An artificial neural network can subgroup pain drawings based on dermatomes.
Türp, Kowalski, Stohler (237) *	2000	Female patients with temporomandibular pain	Generic pain intensity ratings may provide a better picture than site-specific intensity ratings.
Ghinea et al. (238) * §	2002		Geographical information systems are proposed as a method to visualize and analyze pain drawings.
Gagliese, Melzack (239)	2003	Patients with chronic pain	Age differences are identified in the selection of pain quality descriptors.
Bertilson, Grunnesjö, Strender (240) *	2003	Patients with neck and shoulder pain	Some clinical tests may not be reliable. Knowledge of the medical history, including pain drawings, may improve the prevalence of clinical findings.
Masferrer, Prendergast, Hagell (51) *	2003	Patients with neck, low-back or radicular referred pain	Colored pain drawings are as useful as black and white drawings.

North et al. (241) #	2003	Patients with spinal cord stimulator	Automated and self-adjustable spinal cord stimulators are more effective and efficient than the traditional manually adjusted method.
Jamison, Fanciullo, Baird (242)	2004	Patients with chronic pain	A computerized pain assessment program can identify differences in pain intensity and location among patients and health individuals.
Hwang et al. (243) ¤	2005	Healthy participants	Experimentally evoked referred pain patterns resemble dermatomes.
Gibson, Frank (244) *	2005	Electric-powered wheelchair users	Wheelchair users may benefit from using visual analogues scales and pain drawings to assess their pain.
Slipman et al. (245) ¤	2005	Patients with neck pain	Development of disc symptom provocation maps.
Cornwall. John Harris, Mercer (246)	2006	Healthy participants	Experimentally evoked local and referred pain patterns description.
Friedrich, Gittler, Pieler-Bruha (247)	2006	Patients with osteoporotic vertebral fractures	The pain location may be misleading towards the location of the fracture.
Carnes et al. (248)	2007	General population in the UK	Chronic pain located in a single site is less common than multi-site location.
Linder, Svensson (249)	2007	Long-term sick-listed patients	A combination of depression severity and pain extent can be a useful to assess rehabilitation needs.
Ghinea et al. (62) * #	2008		Development of 3-D pain drawings
Thompson et al. (250) *	2009	Patients with chronic or frequent knee pain	Knee pain can be location can differ, suggesting a variety of pain sources.
McClish et al (251)	2009	Patients with sickle cell disease	Pain sites and location vary in frequency by age.

Wenngren, Stålnacke (65)	2009	Patients with chronic pain	Quantification of the pain area using a computerized assessment of pain drawings.
Felix et al. (252)	2010	Patients referred for spinal surgery	Quantitative computerized pain drawings can be a useful clinical tool.
Jud et al. (253) #	2010	Breast cancer survivors	Body charts with a breast outline can assist to visualize pain areas.
Persson, Garametsos, Pedersen (254)	2011	Patients with chronic pain	Good intra-rater reliability of a computer-aided pain area quantification.
Elson et al. (255) #	2011	Patients with knee pain	Development and validation of a photographic knee pain map.
Jamison et al. (64) *	2011	Patients with chronic pain	Three-dimensional pain mapping is a reliable method to report pain location.
Alonso-Blanco et al. (256) §	2012	Female patients with myofascial temporomandibular pain and fibromyalgia syndrome	Identification of differences in the location of areas of referred pain.
Egloff et al. (180) §	2012	Patients with somatoform-functional pain	Identification of drawing criteria to use pain drawings as a screening tool.
Pierce et al. (257) #	2012	Pregnant women	High prevalence of lumbo-pelvic pain.
Renner et al. (258)	2012	Patients with endometriosis	Development of endometriosis pain maps.
Chatterton et al. (259)	2013	Patients with foot pain	Reliable repeatability scores of foot pain drawings.
Prins, van der Wurff, Groen (132)	2013	Patients with chronic low-back pain with and without referred leg pain	Patients with referred leg pain have more intense pain, higher disability scores, and physical health than those without.

Jaatun et al (63) #	2013	Patients with advanced-stage cancer	iPad-based pain assessment has better results than pen-to-paper and laptop-based assessments.
Southerst et al. (260) #	2013	Patients with whiplash-associated disorders	Good inter-examiner reliability of pain drawings acquired from pen-to-paper and electronic body charts.
Gerhardt et al. (140)	2014	General population in Germany	Patients with chronic back pain may also have pain sites located outside the back.
Gumina et al. (261)	2014	Patients with postero-superior rotator cuff tear	Development of pain distribution maps for rotator cuff tears.
Spyridonis et al. (201) *	2014	Wheelchair users and clinicians	Development of a virtual reality application for the assessment of pain.
Tucker et al. (262) *	2014	Healthy participants	Description of experimentally evoked pain intensity, location, depth, and quality in different low-back muscles.
Barmettler et al. (263)	2015	Patients with migraine headaches	Description of spatiotemporal pain patterns and quality descriptors.
Nickel et al. (264)	2015	Female patients with interstitial cystitis/bladder pain syndrome	Identification of two different pain pattern phenotypes.
Barbero et al. (75)	2015	Patients with chronic back and neck pain	Digital pain drawings have a good test-retest reliability.
Jaatun et al. (71) #	2015	Patients with advanced-stage cancer	Development of a web-based pain drawing solution, as well as design guidelines for software development.
Torstesson et al. (265)	2015	Female patients with chronic pelvic pain	Description of referred pain patterns.
Van Hecke et al. (266)	2015		Consensus for neuropathic pain phenotyping.

Boudreau et al. (61)	2016	Patients with chronic neck pain	Touchscreen acquired pain drawings are as reliable as pen-to-paper. Three-dimensional body charts are more accurate than 2-D.
Tesarz et al. (42)	2016	Patients with chronic low-back pain	Description of the stable or spread of pain extent over time.
Van Ginckel et al (267)	2016	Patients with medial tibiofemoral osteoarthritis	Diffuse pain location associated with more severe and physical dysfunction than pain isolated to the medial aspect
Hawkins et al. (268)	2016	Patients with orofacial pain	Patients report multiple pain sites outside the orofacial area.
Lluch Girbés et al. (127)	2016	Pre-operative patients with knee osteoarthritis	Widespread pain distribution is associated with some central sensitization signs.
Falla et al. (269)	2016	Patients with whiplash-associated disorders	Widespread pain extent is associated with disability, depression, and self-efficacy.
Egsgaard et al. (74) * #	2016	Female patients with chronic pain	Gender-specific body charts may facilitate more accurate pain communication.
Poulsen et al. (270)	2016	Patients with hip osteoarthritis	Description of common pain distribution.
Zhang et al. (271) §	2016	Datasets from multiple patients	Assessment of machine learning methods for diagnosis prediction.
Barbero et al. (144)	2017	Female patients with fibromyalgia syndrome	Pain extent is associated with pain intensity.
Boudreau, Kamavuako, Rathleff (76) §	2017	Patients with patellofemoral pain	Identification of symmetrical and non-symmetrical pain distribution patterns.
Candela et al. (272)	2017	Patients with adhesive capsulitis	Description of most common pain distribution pattern.

Cruder et al. (18)	2018	Musicians	High prevalence of pain, and correlation between pain extent and disability.
Doménech-García et al. (117)	2018	Pain-free patients recovering from a shoulder fracture	Pressure-induce pain is larger in patients recovering from fracture than in healthy participants.
Boudreau et al. (20) §	2018	Patients with patellofemoral pain	Identification of distinct Anchor, hook, and ovate pain distribution patterns.
Rio et al. (273)	2018	Australian rules football players	Self-reported pain drawings are more reliable than clinician pain drawings.
Neubert et al. (274)	2018	Chronic pain patients and clinicians	Development, evaluation, and usability of a tablet-based software app to acquire pain drawings and related symptoms.
Shaballout et al. (19) §	2018	Patients in acute pain	Electronic pain drawings can improve the patient-clinician communication.
Wallace et al. (275) §	2018	Patients with chronic pain	Development of a pain drawing compound score.
Swinnen et al. (276)	2018	Patients with axial spondyloarthritis	Females are more likely to report widespread pain than men.
Riis et al. (131)	2019	Patients with chronic neck pan	Pain extent is associated with disability, depression, and clinical tests.
Fernández-de-las-Peñas et al. (277)	2019	Female patients with carpal tunnel syndrome	Pain extent is not associated with physical or psychological variables.
Caseiro et al. (70)	2019	Patients and clinicians	Clinicians have a good reliability to reproduce pen-to-paper pain to digital pain drawings.
Galve Villa et al. (77) * # ¤	2020	Healthy participants	Self-adjustable animations may be a useful tool to quantify changes in quality descriptors.
Galve Villa et al. (143) #	2020	Participants with chronic non-malignant spinally referred pain	The pain and discomfort intensity and extent fluctuate as captured remotely over a prolonged period.

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